

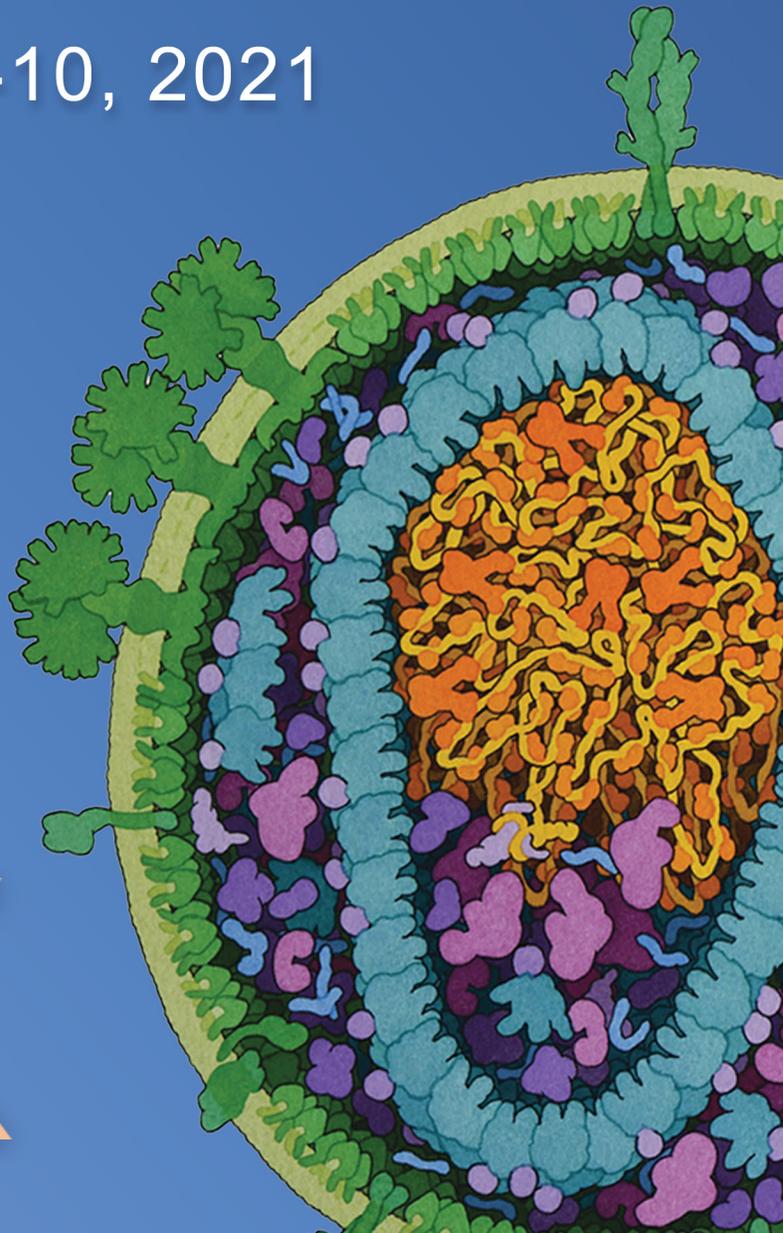
# ABSTRACT eBOOK

*virtual*

# CROI 2021

Conference on Retroviruses  
and Opportunistic Infections

MARCH 6-10, 2021



 **IAS-USA**  
International Antiviral Society-USA



# CONTENTS

|   |            |
|---|------------|
| <b>ABSTRACT PROCESS .....</b>   | <b>2</b>   |
| <b>ORAL ABSTRACTS .....</b>   | <b>4</b>   |
| <b>SCIENCE SPOTLIGHTS™ .....</b>  | <b>63</b>  |
| <b>DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH INELIGIBLE COMPANIES.....</b> | <b>309</b> |
| <b>AUTHOR INDEX.....</b>  | <b>314</b> |

# ABSTRACT PROCESS

## Scientific Categories

- 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
- G. Clinical Pharmacology in Adults
- H. Therapy: Preclinical 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
- R. Epidemiology of HIV and COVID-19 in Adults
- T. HIV and COVID-19 Testing in Adults: New Diagnostics, Population Studies, and Scale-Up
- V. HIV Prevention and COVID-19 Interventions in Adults
- 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

## Abstract Content

Author names, institutions, titles, and abstracts in the CROI Program Information Guide, Abstract eBook, Virtual 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 the 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.

## Presenting Author Responsibilities

Visit the [Invited Presenter](#), [Oral Abstract Presenter](#), and [Science Spotlight Presenter](#) webpages for information regarding presenter responsibilities.

## Embargo Policies and Social Media

All research presented at CROI 2021 is embargoed until the conclusion of the study's presentation at the conference. CROI Conference embargo policies are designed to ensure that the entire scientific community receives full and accurate information about research presented at the conference simultaneously. Embargo violations can lead to misinformation or incomplete information about research presented at the conference. CROI requests that all conference participants familiarize themselves with these embargo policies, which will be strictly enforced.

- For Oral Abstract presentations, if a study is presented from 2:15 PM to 2:30 PM, as part of a session that begins at 2:00 PM and ends at 3:00 PM, the embargo on that study lifts at 2:30 PM
- Embargoes on Science Spotlight™ presentations lift when the Science Spotlights™ become available to participants, on Saturday, March 6, 2021, at 12:01 AM Eastern Time
- If a study to be presented at CROI 2021 is included in an official CROI press conference that takes place before the scheduled presentation of the study, the embargo on that study lifts at the conclusion of the press conference panel in which the study is featured

No public dissemination of research information from the conference is permitted prior to the lifting of the conference embargo. CROI embargo policies apply to any public dissemination of research information presented at the conference, including electronic publications (eg, blogs) or social media (eg, Twitter, Instagram, Facebook).

Individuals or organizations that violate the conference embargo policy may have their conference credentials revoked and may forfeit the opportunity to participate in future conferences.

For additional information regarding the CROI embargo policies, visit the [Embargo and Press Release Policies](#) webpage.

## Abstract Review Process

For information, visit the [Abstract Guidelines and Submission](#) webpage.

## Statistics for Abstracts

|  |             |
|--|-------------|
| General Abstract Submitted                 | 1050        |
| General Abstracts Accepted                 | 632         |
| General Oral Abstracts Accepted            | 92          |
| General Science Spotlights™ Accepted       | 540         |
| Late-Breaking Abstracts Submitted          | 103         |
| Late-Breaking Abstracts Accepted           | 66          |
| Late-Breaking Oral Abstracts Accepted      | 17          |
| Late-Breaking Science Spotlights™ Accepted | 49          |
| <b>Total Abstracts Submitted</b>           | <b>1153</b> |
| <b>Total Abstracts Accepted</b>            | <b>698</b>  |

## All Presenting Authors on Accepted Abstracts

| Region                    | N   | Percent |
|---------------------------|-----|---------|
| Australia                 | 14  | 1%      |
| Central and South America | 14  | 1%      |
| Asia                      | 27  | 3%      |
| Africa                    | 90  | 9%      |
| Europe                    | 237 | 23%     |
| North America             | 635 | 63%     |

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

|                                    |     |
|------------------------------------|-----|
| 1. SARS-CoV-2                      | 161 |
| 2. Adolescents                     | 32  |
| 3. Men Who Have Sex With Men (MSM) | 46  |
| 4. People Who Inject Drugs (PWID)  | 13  |
| 5. Transgender Men or Women        | 7   |
| 6. Women                           | 82  |

Authors have noted specific populations as the focus of their study, if applicable. These indexes are developed for participants with an interest in these areas.

# ORAL ABSTRACTS

## How to cite the abstracts:

Smith I, Jones RM, Peters S, et al. Randomized controlled trial in HIV infection [CROI Abstract 1251]. Abstracts From the virtual CROI 2021 Conference on Retroviruses and Opportunistic Infections. *vCROI 2021 Abstract eBook*. 2021;483.

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

**Serena S. Spudich**, *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 both HIV and SARS-CoV-2. The program will begin with a presentation by Dr Frank Kirchhoff 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 Galit Alter will cover the immune responses (with a particular focus on B- and T-cell responses) against HIV and SARS-CoV-2. Dr Jürgen Rockstroh will outline the most efficient prevention measures for controlling the COVID-19 pandemic and will review new testing technologies as well as therapeutic strategies and currently available SARS-CoV-2 vaccines. In the next presentation, Jean-Michel Molina will address advances in different biomedical strategies for prevention of HIV transmission, with an emphasis on the recent development in preexposure prophylaxis (PrEP) but also some of the emerging strategies to limit SARS-CoV-2 transmission. Finally, Dr Katharine Bar will review advances in characterizing the size and composition of the replication- and rebound-competent HIV-1 reservoirs as well as highlight several 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 vCROI 2021.

### 2 VACCINE NATIONALISM IS KILLING US: HOW INEQUITIES IN RESEARCH AND ACCESS TO SARS-CoV-2 VACCINES WILL PERPETUATE THE PANDEMIC

**Gregg S. Gonsalves**, *Yale University, New Haven, CT, USA*

This presentation will include a conversation among the panelists as they discuss the worldwide struggle for access to antiretroviral therapy and the current battle to ensure everyone is vaccinated against SARS-CoV-2 across the planet. Panelists will describe how coalitions among activists, affected communities, and scientists were crucial for the fight against AIDS and how similar collaborations are vital now in the face of the COVID-19 pandemic. Panelists will discuss the similarities in the challenges for global access to antiretroviral therapy and SARS-CoV-2 vaccines but also how the speed and breadth of the spread of the novel coronavirus present new obstacles to existing institutions (eg, NIH, WHO, GAVI, WTO) and require solutions at far larger scale and established with greater urgency than accomplished for HIV, tuberculosis and malaria to date.

### 3 NEUTRALIZING ANTIBODIES AGAINST CORONAVIRUSES

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

Neutralizing monoclonal antibodies against SARS-CoV-2 are being used as therapeutics against COVID-19. The Bjorkman laboratory is investigating the mechanisms of virus neutralization by human antibodies that bind the SARS-CoV-2 spike protein. Using structural techniques, including single-particle cryo-electron microscopy and X-ray crystallography, the laboratory has solved spike

trimer-antibody structures that allow classifying antibodies with respect to spike recognition and neutralization. They are also designing and testing mosaic nanoparticles that induce broadly cross-reactive antibodies with the goal of creating a pan-coronavirus vaccine that could protect against SARS-CoV-2 and future coronaviruses with the potential to spill over into humans.

### 4 LESSONS FROM THE CONCURRENT HIV/AIDS AND COVID-19 PANDEMICS: A TWO-WAY STREET

**Anthony S. Fauci**, *National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA*

The concurrent COVID-19 and HIV/AIDS pandemics pose unprecedented societal, economic, and public health challenges to nations around the world. The juxtaposition of the HIV/AIDS and COVID-19 pandemics underscores the priority and urgency to accelerate the development and clinical evaluation of prevention and treatment countermeasures. Lessons learned from the HIV/AIDS pandemic inform the discovery and testing of innovative strategies to prevent, treat, and care for individuals with SARS-CoV-2 infection and COVID-19. Similarly, the COVID-19 pandemic highlights that an effective response to the HIV/AIDS pandemic requires a novel coordinated and collaborative global effort of scientists, industry, and community partners to accelerate basic and clinical research as well as implementation science to operationalize evidence-based interventions expeditiously in real-world settings.

### 5 STRUCTURES OF SARS-CoV-2 ANTIBODIES INDUCED BY INFECTION AND mRNA VACCINES

**Christopher O. Barnes**, *California Institute of Technology, Pasadena, CA, USA*

In the space of less than a year, structural biology uncovered structure-function details for many of the proteins encoded by SARS-CoV-2, the coronavirus that has caused worldwide suffering and more than 1 million deaths since 2019. Remarkably, structures of the SARS-CoV-2 spike trimer were published in March 2020, only about 2 months after the viral sequence was available, aided by previous studies that established how to stabilize coronavirus spikes and the rapid turn-around time for solving structures by single-particle cryo-electron microscopy. Since then, other structures have revealed how spike binds to its angiotensin-converting enzyme 2 (ACE2) receptor, the specificities of polyclonal antibody responses in COVID-19-convalescent individuals, and how monoclonal neutralizing antibodies or designed protein inhibitors bind spike to prevent infection. Taken together, these structures have informed the development of potential therapeutics, including how pairs of monoclonal antibodies are chosen for treatment cocktails and guided structure-based engineering approaches to improve antibody potencies that are effective at lower doses and/or are resistant to viral mutations. With the rapid improvements in microscopes, cameras, and processing techniques, details of individual viral proteins (eg, spikes and ribonucleoproteins) can be resolved in their native context, providing more knowledge for researchers to use against this virus. Here, we will detail studies of neutralizing antibodies against the receptor binding domain induced by both infection by SARS-CoV-2 and by mRNA vaccines. Our data suggest that functionally similar antibodies are raised during vaccination and natural infection, and that the RBDs of spike trimers translated from the mRNA delivered by vaccination adopt both "up" and "down" conformations as observed on structures of trimer ectodomains and trimers on the surface of SARS-CoV-2 virions. Taken together, our work and the work of others illustrate the value of structural biology as a tool to gather information that will aid us in our battle to control the current pandemic and future outbreaks of deadly viruses.

**6 EMERGING CONCEPTS IN HIV-1 RESTRICTION****Edward Campbell**, *Aalborg University Hospital, Aalborg, Denmark*

The ability of HIV-1 to replicate in a target cell depends on its ability to evade the activity of cellular proteins, known as restriction factors, which are capable of inhibiting numerous steps of the HIV-1 replication cycle. In this regard, viruses and their hosts are locked in an evolutionary arms race in which selective pressure on both viruses and the host drives the refinement and expansion of genes that facilitate the evasion or maintenance of the antiviral activity of these proteins, respectively. In this talk, I will provide a survey of the restriction factors known to impact HIV-1 replication and the viral mechanisms used to evade these restriction factors. I will specifically focus on the methodologies used to identify and interrogate these interactions. I will also highlight opportunities afforded by our understanding of the restriction factors that can inhibit HIV-1 infection, or the technologies utilized to identify them, that may be used to interrogate virus/host interactions with other viruses, such as SARS-CoV-2, and highlight early efforts in this area.

**7 SARS-CoV-2 SPECIFIC AND CROSS-REACTIVE T CELL RESPONSES****Daniela Weiskopf**, *University of California San Diego, San Diego, CA, USA*

Understanding adaptive immune responses to SARS-CoV-2 is important for vaccine development efforts, interpreting disease pathogenesis, and calibration of future pandemic control measures. We have developed HLA class I and class II predicted peptides, collected into "Megapools" (MP), to identify SARS-CoV-2-specific CD4+ and CD8+ T cells in coronavirus disease 2019 (COVID-19) convalescent patients. Importantly, we detected SARS-CoV-2 reactive CD4+ T cells in 40–60% unexposed individuals sampled before 2019, implicating pre-existing cross-reactive T-cell memory. Using human blood samples derived pre-2019, we demonstrated a range of preexisting memory CD4+ T cells that are cross-reactive with comparable affinity to SARS-CoV-2 and HCoV-OC43, HCoV-229E, HCoV-NL63, or HCoV-HKU1. Thus, variegated T-cell memory to common cold coronaviruses may underlie at least some of the extensive heterogeneity observed in COVID-19 clinical and subclinical disease.

**8 ARTIFICIAL INTELLIGENCE—INSPIRED ANTIBODY ENGINEERING****Sai Reddy**, *ETH Zurich, Zurich, Switzerland*

Machine learning and deep learning are part of a family of tools related to artificial intelligence and represent an emerging field of information and computer science that uses large data sets to extract features and representations. Antibody discovery and engineering is reliant on experimental platforms of high-throughput expression and screening of libraries. Here, I will describe how researchers are using machine and deep learning to assist in antibody engineering experiments and thus move beyond experimental screening. One area that I will highlight in particular is related to deep sequencing of natural antibody repertoires (derived from B cells of humans and mice), which has become a promising and powerful tool in basic immunology, immunodiagnosics, and the drug discovery process. However, identification of relevant information in these large datasets remains challenging. I will explain how deep learning is being used to identify patterns of antigen-specificity from antibody repertoires. Approaches such as unsupervised clustering and deep generative modeling are then being used to elucidate the antibody sequence space by generating thousands of novel and functional variants *in silico*. In addition deep learning is also being used to interrogate and predict antigen-specificity from a massive diversity of antibody sequence space from synthetic antibody repertoires (derived from surface display libraries). With its scalability and capacity to interrogate a vast protein sequence space, deep learning offers great potential for antibody discovery, engineering, and optimization.

**9 MAKING SENSE OF STUDY DESIGN DIFFERENCES BETWEEN COVID-19 PLATFORM TRIALS****Lori Dodd**, *National Institutes of Health, Bethesda, MD, USA*

Platform trials are multi-arm studies that allow experimental agents to enter and exit a study over time. Sharing a control arm can provide efficiency gains in terms of a smaller total sample size. Many trialists have recommended platform trials for COVID-19 treatment studies largely due to their potential to reach conclusions faster. However, not all platform trials are created equally. Important design choices that alter study rigor include study endpoints, whether to use a placebo, whether to use response-adaptive randomization, whether to allow comparisons with nonconcurrent controls, how many agents to study, and when to drop/add study agents. In this talk, I will provide

a framework to critically evaluate study design decisions behind COVID-19 treatment trials. This framework will be applied to the major trials as a way to rank quality of study results.

**10 DESIGN OF CURRENT AND FUTURE COVID-19 VACCINE EFFICACY TRIALS****Holly Janes**, *Fred Hutchinson Cancer Research Center, Seattle, WA, USA*

Rapid development and deployment of safe and effective COVID-19 vaccines for the global population is a public health imperative. We will overview the key statistical design elements of the first-generation US-government-funded vaccine efficacy trials, including the rationale and choice of endpoints, success criteria, triggers for analysis, and design adaptations following early evidence of efficacy. The implications of the emerging results for second-generation trials to evaluate additional vaccine candidates and to complete the profile of existing vaccines will be discussed.

**11 RAPID GENOMIC SEQUENCING FOR MANAGEMENT OF COVID-19****Kwok-Yung Yuen**, *University of Hong Kong, Pok Fu Lam, Hong Kong*

Rapid target enrichment sequencing documented the first case of reinfection by SARS-CoV-2. The reinfecting virus has 24 nucleotides (12 amino acids) difference with one stop codon leading to a deletion of 58 amino acid at orf8. Moreover the reinfecting virus is located on a different branch from the first infecting strain on the phylogenetic tree. Retrieval and testing of his initial serum showed that the neutralizing antibody titre of 40 has dropped within 5 months to below 10 at the time of reinfection. Within 3 days after reinfection, his serum antibody level started to rise, and it reached 3200 within 8 days. Besides differentiating reinfection from persistent infection, rapid genome sequencing has been used to demonstrate person-to-person transmission in a family cluster of COVID-19. This technology is also useful for the investigation of hospital outbreak, which led to the refinement of admission SARS-CoV-2 screening strategy. In terms of public health policy, phylogenomics has demonstrated the importance of border control to prevent virus entry and the necessity of stringent social distancing measures to prevent virus dissemination in the community. The close monitoring for virus mutants has led to the discovery of highly transmissible mutants such as the Spike D614G and N501Y and other Spike mutants that may have varying degrees of resistance to remdesivir, therapeutic antibodies, and vaccines.

**12 COVID-19: A HOSPITALISED UNWELL PATIENT WITH PNEUMONITIS****Sanjay Bhagani**, *Royal Free Hospital, London, UK*

This case study will focus on clinical presentation and evidence-based management of patients with severe COVID-19. Risk factors for mortality and predictors of severity will be discussed. In addition to best standard of care, we will explore evolving data on the use of antiviral and immune-modulatory therapy.

**13 CRITICAL CARE OF COVID-19****Janhavi Athale**, *Mayo Clinic Arizona, Phoenix, AZ, USA*

The novel coronavirus of 2019 (SARS-CoV-2) has resulted in an increased incidence of patients admitted to intensive care units (ICUs). On average 5 percent (ranges of 3–80% have been reported) of patients with COVID-19 require ICU admission. Unfortunately, a vast majority of these ICU patients contribute to the mortality seen with this disease. The chief reason for ICU admission in COVID-19 is hypoxia. Infection with SARS-CoV-2 results in inflammation and damage to the lung parenchyma via the receptor angiotensin-converting enzyme 2 (ACE2) on type II pneumocytes. The resulting lung damage presents as a clinical syndrome: Acute Respiratory Distress Syndrome (ARDS). Thus, the management of COVID-19-associated ARDS has been adopted from prior studies that have assessed interventions in ARDS. Treatment of ARDS remains complex with very few studies demonstrating mortality benefits. In addition to hypoxia associated with COVID-19, the presentation will address 2 additional features of COVID-19: cytokine storm and immunothrombosis or hypercoagulability associated with COVID-19. The cytokine storm, or hyperinflammatory syndrome, associated with COVID-19 has been attributed to the exaggerated immune response to the virus that results in multiorgan dysfunction. Treatment of this hyperinflammatory syndrome has been extrapolated from cytokine release syndrome (CRS) seen in other diseases. The increased incidence of venous thromboembolism (VTE) and additional clotting seen with COVID-19 has resulted in aggressive anti-coagulation strategies in treatment of this disease. We are continuing to obtain new data on COVID-19, and the management decisions can be very institution- or provider-dependent.

The goal of this presentation is to review the current data and outline some of the salient features in treatment of critically ill patients with COVID-19.

#### 14 IMAGING VIRAL LIFE CYCLES

**Hans-Georg Krüsslich**, Heidelberg University, Heidelberg, Germany

Understanding viral replication and spread for a long time depended on bulk analysis of infected cells and mostly used transformed cell lines in tissue culture. Advances in imaging methods and labeling tools more recently allowed studying individual infection events and specific stages of the infection cycle. This includes analysis of trafficking and morphological changes of individual viral components at high spatial and/or temporal resolution also using primary target cells. In parallel, advances in (cryo) electron microscopy and tomography not only allowed visualizing structural components of the extracellular virion at near atomic resolution but also yielded structural information on viral components inside infected cells and on their interaction with host cell components. On the other hand, development of organoid systems and other 3D culture systems in combination with light sheet microscopy and other methods allowing analysis of virus infection in complex 3D cultures yielded important new insights on viral infections more similar to the real in vivo situation; certain aspects of viral replication and spread could even be studied in living animals, applying 2-photon-microscopy. This overview will summarize and discuss recent advances achieved by improved imaging technologies with a major focus on HIV-1, but also addressing aspects important for other viruses.

#### 15 DISPARITIES IN HEALTH: FROM HIV TO COVID-19 AND BEYOND

**James E. Hildreth**, Meharry Medical College, Nashville, TN, USA

The 2 ongoing pandemics in the US, COVID-19 and HIV/AIDS, have several parallels including significant racial disparities in disease burden. These parallels will be discussed along with a consideration of the social determinants of health underlying these inequities.

#### 16 SARS-CoV-2 EVOLUTION IN POPULATIONS AND INDIVIDUALS

This highly interactive session begins with a brief overview of the issue or controversy. Each of the scientific experts offer their opinions or observations in a 5-minute summary, followed by a 30-minute spirited discussion among the panel members. The moderator will bring in comments and questions from the audience. This session will address the evolution of SARS-CoV-2 vs HIV at the population level, viral and antibody evolution in populations, the origin and spread of highly transmissible variants of SARS-CoV-2, and the selection of neutralization-resistant SARS-CoV-2 mutants.

#### 17 CASE-BASED DISCUSSION ON WEIGHT GAIN IN HIV AND ANTIRETROVIRAL THERAPY

This interactive session will discuss current controversies about the causes and consequences of weight gain during antiretroviral therapy (ART) using a case-based format. Specific topics that will be covered include: 1) the relative contributions of particular ART drugs/classes and reversal of viral replication/inflammation to weight gain, 2) the pathophysiology of weight gain during ART, 3) the impact of ART-associated weight gain on type 2 diabetes risk, and 4) how these issues are perceived and managed in diverse populations, including children, pregnant women, and people with HIV in low-income countries.

#### 18 CONTACT TRACING IN CONTROLLING EPIDEMICS: IS THE JUICE WORTH THE SQUEEZE?

This interactive session will begin with 3 presentations by experts describing the role, methodology, and ethical issues of contact tracing. Following the presentations, there will be a moderated discussion and responses to comments and questions from the audience.

#### 19 LIVE-CELL IMAGING: CAPSID TRAFFICKING TO THE NUCLEUS

**Barbara Müller**, Heidelberg University, Heidelberg, Germany

Over the past decade, the role of the mature HIV-1 capsid in viral replication has undergone a major paradigm shift. It became increasingly clear that the simple view of the capsid as a mere proteinaceous wrapper encasing the viral genome, which becomes obsolete soon after cytosolic entry, is incorrect. Today it is no longer debated that not only the CA protein but the capsid itself is involved in post-entry events subsequent to cytosolic entry. However, its precise function is incompletely understood and such questions as "when, where, and how does capsid uncoating occur?" are controversially discussed. This presentation focuses on modern fluorescent labeling and imaging approaches that contribute to our current understanding of post-entry events and the fate and functions

of the viral capsid. Recent work from several laboratories has shed light on pathways and mechanisms involved in trafficking of viral complexes to and through the nuclear pore, resulting in emergence of the assembled capsid as a master organizer of HIV-1 post entry. It mediates numerous interactions with the host cell environment, acting as a reaction container, as a protective shield around the nascent viral DNA, and as a transport vehicle that mediates targeted transfer of subviral complexes, from the site of cytosolic entry to integration of the proviral DNA in the host cell nucleus. Although open questions remain, recent studies from us and others have begun to resolve apparent discrepancies that had led to discordant conclusions in the past. These studies open the door toward a clear understanding of molecular events during the post-entry phase of HIV-1 replication.

#### 20 LIVE-CELL IMAGING OF HIV-1 NUCLEAR IMPORT, UNCOATING, AND PROVIRUSES

**Vinay K. Pathak**, National Cancer Institute, Frederick, MD, USA

The HIV-1 mature conical core, composed of ~250 capsid protein (CA) hexamers and ~12 pentamers, must disassemble (uncoat) and the viral DNA must enter the nucleus before it can integrate into the host genome. For the past 4 decades, retroviral uncoating has been widely believed to occur in the cytoplasm, and some recent studies have proposed that uncoating occurs at the nuclear envelope (NE) just prior to nuclear import. Studies of uncoating have been hampered by an inability to accurately quantify the amount of CA associated with viral reverse transcription/preintegration complexes, and an inability to study rare infectious viral cores in a vast majority of non-infectious viral cores. We recently developed methods to directly label CA with green fluorescent protein (GFP) and track viral cores in infected cells by live-cell microscopy. In addition, we developed methods to identify infectious viral cores that led to the formation of transcriptionally active proviruses. In striking contrast to the prevailing models of nuclear import and uncoating, our results showed that infectious viral cores in the nucleus are intact and complete reverse transcription in the nucleus before uncoating. Recent studies from other groups supporting this model have shown that viral cores in the nucleus are largely intact, that reverse transcription requires an intact capsid and that reverse transcription is completed in the nucleus. We also probed the mechanism of viral core nuclear import and showed that intact viral cores gain nuclear entry through a mechanism involving interactions at the NE with the host protein cleavage and polyadenylation specificity factor 6 (CPSF6). Using GFP as a capsid content marker, we have recently observed that nuclear capsids retain their integrity and maintain a separation between the viral core contents and the nuclear environment until <1.5 hours before integration. These observations fundamentally change our current understanding of HIV-1 post-entry replication events including mechanisms of nuclear import and uncoating as well as reverse transcription, integration, and evasion of innate immunity.

#### 21 VISUALIZATION OF HIV-1 CAPSID-DEPENDENT REPLICATION IN VITRO

**Barbie Ganzer-Pornillos**, University of Virginia, Charlottesville, VA, USA

HIV-1 initiates receptor-mediated entry of the virus core particle into the cytoplasm of a host cell. This core particle is organized by a fullerene capsid shell, which houses the viral RNA genome and its associated replicative enzymes. Upon entry, the capsid facilitates reverse transcription, shields the viral nucleic acids from host defense sensors, and coordinates interactions with many different host factors to deliver the genome to the nucleus. A variety of studies now appear to be converging upon a model in which reverse transcription initiates soon after entry but does not become complete until the core is at the nucleus, whereupon the capsid uncoats and releases the pre-integration complex in close proximity to the host chromosomes. In situ mechanistic and structural studies of these processes remain challenging because these operations are executed by individual viral particles deep within cells. Here, I will discuss studies in which we reconstitute endogenous reverse transcription in vitro from HIV-1 cores that are released from permeabilized virions. This cell-free system allowed us to monitor the core structure throughout the entire process of replication and uncovered an important role for the capsid in templating replication. Capsid persistence during reverse transcription appears to be dictated not only by the intrinsic stability of the CA lattice but is also positively and negatively modulated by host factors. We are now expanding this reconstitution system to include the nuclear import steps and eventual integration into authentic human chromosomes.

## 22 LENCAPAVIR (GS-6207): FIRST CLINICALLY ACTIVE LONG-ACTING INHIBITOR OF HIV CAPSID

**Tomas Cihlar**, *Gilead Sciences, Inc, Foster City, CA, USA*

A program building on prior extensive structural and functional characterization of HIV capsid and spanning a decade of drug discovery work yielded lenacapavir (LEN; GS-6207), a small molecule inhibitor targeting several critical functions of HIV capsid. LEN binds at a conserved interface between capsid monomers and interferes with protein interactions essential for multiple phases of the HIV replication cycle, including both the assembly and disassembly of capsid core as well as capsid nuclear trafficking. LEN exhibits in vitro antiviral activity at picomolar concentrations against all subtypes of HIV, including strains resistant to other antiretroviral classes. A potent antiretroviral activity of a single dose LEN has been demonstrated in phase 1b viral dynamics study conducted in treatment-naïve people living with HIV, and several ongoing clinical studies are evaluating the efficacy of LEN administered once every 6 months subcutaneously in combination with other antiretroviral agents. In addition, emerging efficacy data from non-human primates support further investigation of LEN as a long-acting agent for pre-exposure prophylaxis.

## 23 FROM GENOME TO FUNCTION: PHENOTYPIC CHARACTERISATION OF PANDEMIC SARS-CoV-2 VARIANTS

**Volker Thiel**, *University of Bern, Bern, Switzerland*

SARS-related coronaviruses have been known for several years to circulate in diverse bat species and they are known to have the potential to infect humans. The zoonotic emergence of SARS-CoV-2 exemplified that these viruses also have pandemic potential. Here I will show how we can reconstruct SARS-CoV-2 in order to obtain molecular clones for functional and phenotypic studies. Based on this novel reverse genetic system it is now possible to rapidly reconstruct SARS-CoV-2 and to phenotypically characterize SARS-CoV-2 variants that emerge during the pandemic in real-time.

## 24 IMMUNE EVASION STRATEGIES BY SARS-CoV-2: NSP1 AND BEYOND

**Konstantin Sparrer**

*Ulm University Medical Center, Ulm, Germany*

The human innate immune system represents a powerful first line of antiviral defenses. Incoming viral pathogens are quickly detected by dedicated germ-line encoded sensors, called pattern recognition receptors. For example, intracellular RNA viruses, like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are detected by RIG-like receptors such as RIG-I and MDA5. Activation of these sensors initiates signaling cascades that ultimately lead to the secretion of different types of interferons (IFNs) and other pro-inflammatory cytokines. Upon binding to their respective receptors, these cytokines induce a transcriptional program setting infected and neighbouring cells in an antiviral state. In parallel, other antiviral mechanisms, such as autophagy, are mounted. Autophagy is capable of targeting viruses and viral components for lysosomal degradation, facilitating their removal from a cell as well as immune recognition. Eventually, activation of the innate immune system stimulates the adaptive immune system. However, successful viral pathogens like SARS-CoV-2 have evolved intricate strategies to evade or even subvert innate immunity. Recent research has shown that most of the approximately 30 proteins that are encoded by SARS-CoV-2 manipulate and disarm innate immune defences. Major innate immune antagonists include the non-structural proteins (Nsp) 1 and 3 as well as the accessory proteins ORF3a and ORF6. Nsp1 blocks cellular ribosomes, consequently preventing translation of antiviral proteins including IFNs. Nsp3 attenuates the type-I IFN response by removing the post-transcriptional modifier ISG15 from the immune sensor MDA5 and the transcription factor IRF3. ORF3a was reported to suppress autophagic degradation by blocking the turnover, while ORF6 interferes with nuclear translocation of transcription factors required for the IFN response. Here, I will give an overview on innate immune evasion strategies employed by SARS-CoV-2 and highlight selected molecular mechanisms.

## 25 SHARED VULNERABILITIES AND DIFFERENT COUNTERMEASURES OF HIV AND SARS-CoV-2

**Eric O. Freed**, *National Cancer Institute, Frederick, MD, USA*

Viruses rely heavily on host cellular machinery to replicate. In turn, cells have evolved elaborate defense mechanisms to impede virus replication. Numerous cellular proteins, often referred to as inhibitory or restriction factors, are central components of the innate immune response that serves as the first

line of defense against invading pathogens. In recent years, several families of host proteins have been shown to inhibit the function of a wide range of viral envelope glycoproteins, thereby blocking virus infection. These include the IFITM proteins, guanylate binding protein 5, the SERINC proteins, and the membrane-associated RING-CH (MARCH) family of RING-finger E3 ubiquitin ligases. MARCH proteins downregulate cell-surface proteins involved in adaptive immunity. The RING-CH domain of MARCH proteins is hypothesized to ubiquitinate the cytoplasmic tails (CTs) of target proteins leading to their proteasomal or lysosomal degradation. Three MARCH proteins (MARCH1, 2, and 8) have recently been reported to target the HIV-1 envelope glycoprotein (Env) and vesicular stomatitis virus G glycoprotein (VSV-G), thereby impairing the infectivity of HIV-1 virions bearing these glycoproteins. We show that MARCH protein expression is rapidly induced by interferon (IFN) treatment and that the antiviral activity of MARCH proteins extends to the Ebola virus glycoprotein (EboV-GP) and the SARS-CoV-2 spike (S) protein. We observe that MARCH protein targeting of VSV-G is to a large extent CT-dependent. In contrast, MARCH-protein targeting of HIV-1 Env, EboV-GP, and SARS-CoV-2 S protein does not require the CT, indicating that MARCH-mediated inhibition of these viral glycoproteins is likely indirect and via targeting a cellular host factor(s) involved in glycoprotein trafficking. Confocal microscopy data demonstrate that MARCH proteins are able to trap the viral glycoproteins in an intracellular compartment bearing lysosomal markers. These results clarify the mechanism by which MARCH proteins antagonize viral glycoproteins and provide insights into the antiviral role of cellular inhibitory factors in Env biogenesis, trafficking, and virion incorporation.

## 26 IMMUNE RESPONSES TO SARS-CoV-2

**Akiko Iwasaki**, *Yale University, New Haven, CT, USA*

The clinical presentation of COVID-19 involves a broad range of symptoms and disease trajectories. Understanding the nature of the immune response that leads to recovery over severe disease is key to developing effective treatments for COVID-19. In this talk, I will discuss immune responses in COVID-19 patients with moderate and severe disease. I will compare viral load, immune phenotype, and cytokines that are predictive of mortality and discuss signatures of cytokines and growth factors that associate with recovery vs disease exacerbation. I will also discuss sex differences in immunity to SARS-CoV-2 and how such differences correspond to disease outcomes.

## 27 THE POTENTIAL OF LONG-ACTING INJECTABLE DRUGS FOR PREVENTION AND TREATMENT OF TB

**Eric Nuermberger**, *The Johns Hopkins University, Baltimore, MD, USA*

More effective and readily implementable preventive therapy for tuberculosis (TB) is a critical unmet need in order to end the TB epidemic. Long-acting injectable formulations of TB drugs have great potential to meet this need, especially in pregnant individuals and children. This presentation will describe how long-acting injectable TB drugs could address important obstacles in the prevention and treatment of tuberculosis, illustrate an example where proof-of-concept has been achieved, and discuss future directions and challenges for further development.

## 28 PREGNANCY, HIV, AND TUBERCULOSIS: CURRENT PRACTICES AND RESEARCH OPPORTUNITIES

**Jyoti S. Mathad**, *Weill Cornell Medicine, New York, NY, USA*

Tuberculosis is a leading cause of maternal mortality, especially among women living with HIV. Women are most likely to develop active tuberculosis during and immediately after pregnancy. But the prevention and management of tuberculosis during pregnancy remain contentious, and national guidelines vary widely owing to insufficient data. This presentation will review: (1) the global burden of tuberculosis in women of reproductive age; (2) how pregnancy and the postpartum period affect M. tuberculosis immunology in women with and without HIV; (3) how to screen and treat pregnant women for tuberculosis infection, including data on isoniazid preventive therapy, rifampentine-containing regimens, and potential drug-drug interactions with antiretrovirals; (4) how to diagnose and treat pregnant women for tuberculosis disease, including drug-resistant tuberculosis; and (5) high-priority research areas for tuberculosis research in pregnant and postpartum women.

**29 ADVANCES IN PEDIATRIC TUBERCULOSIS PREVENTION AND TREATMENT**

**Nicole Salazar-Austin**, *The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

The overlapping HIV and tuberculosis (TB) epidemics have been devastating for children and adolescents living with HIV. This group continues to suffer disproportionately high TB-associated mortality. Poorly implemented TB prevention programming, limited sensitivity and specificity of diagnosis tools, and interactions with antiretroviral and anti-TB drugs continue to plague prevention and management of TB/HIV coinfection in children and adolescents living with HIV. This presentation will discuss recent advances and continued challenges in pediatric TB diagnosis, treatment, and prevention for both children and adolescents living with HIV and HIV-exposed uninfected (HEU) children.

**30 IMPACT OF COVID-19 PANDEMIC ON HIV AND TUBERCULOSIS: WHO PERSPECTIVE**

**Souyma Swaminathan**, *World Health Organization, Geneva, Switzerland*

The COVID-19 pandemic has infected more than 100 million people, killed more than 2.4 million, and had a major impact on the health system's ability to deliver essential health services. The impact of COVID-19 on other infectious diseases such as HIV and tuberculosis (TB) has been immense, particularly in low-resource settings with high HIV and TB burden. Ongoing TB data collection and analysis from 200 countries have shown reduced access to care in outpatient and inpatient facilities, impacting the entire care cascade, including prevention, with case detection rates dropping by over 50% in some endemic countries in 2020. By its negative impact on poverty and malnutrition, it is possible that TB incidence could actually increase, strengthening the argument for robust prevention measures. The pandemic has caused significant disruption to HIV programs by limiting access to life-saving antiretrovirals due to movement restrictions, local stockouts, and decrease in uptake of facility-based services. These disruptions are also expected to have reverted some of the progress made in preventing vertical transmission of HIV, resulting in increased numbers of paediatric HIV infections. Therefore, strengthening systems for the maintenance of HIV, TB/HIV, and TB services is an urgent need in many high-burden countries. Although COVID-19 has challenged TB and HIV programmes, it has also offered several lessons, including how we join forces, innovate, and accelerate research and development. Some examples are the use of digital tools for contact tracing, use of AI-based diagnostic algorithms, widespread sharing of genomic sequence data to track virus evolution and emergence of new variants, and large multisite clinical trials to test new therapeutics and vaccines. The development and evaluation of new TB and HIV treatments and vaccines should learn from the past year of accelerated development and explore new models of public-private partnership for the development of global public goods. Despite progress, vulnerable populations such as children and pregnant women continue to lag behind innovations for TB and HIV, and these groups need to be included in clinical trials much sooner. Finally, we need to expand and strengthen the integration of services within the primary healthcare platform, optimizing differentiated service delivery, community engagement and the use of digital technologies to reach those most at risk of TB and HIV with screening, prevention, diagnosis, and treatment.

**31 DOES HIV IMPACT COVID-19 SUSCEPTIBILITY OR SEVERITY?**

**Julia Del Amo**, *Ministry of Health, Madrid, Spain*

In the early days of the COVID-19 pandemic, the HIV community became preoccupied that COVID-19 could be more severe in people with HIV (PWH) because of immunodeficiency, higher prevalence of comorbidities and immunosenescence, which had been associated with poorer COVID-19 outcomes. Nonetheless, HIV was not initially identified as disproportionately prevalent in hospitalized patients with COVID-19, an observation that still holds. It was also argued that because of immune dysfunction, PWH could be less likely to develop the harsh immunologic response that complicates COVID-19 and that some antiretroviral drugs could impair SARS-CoV-2 replication. Numerous studies have been published since, some with apparently contradictory conclusions. Different epidemiological designs and information sources have been used, from case reports to population-based cohorts. Some have compared PWH to people without HIV; others have made comparisons across PWH with different characteristics. Some have reported higher COVID-19 mortality in PWH compared with people without whereas others have not, but there are important differences in the comparison populations and confounders

adjusted for. Associations between CD4 cell counts and COVID-19 outcomes are not consistent. The role of protease inhibitors on SARS-CoV-2 RNA-dependent RNA-polymerase has been ruled out, but evidence of effects of tenofovir disoproxil fumarate is accumulating from observational studies. Some of the well established risk factors for SARS-CoV-2 acquisition—high mobility and social interaction, belonging to racial and ethnic minorities and socially disadvantaged groups—are more common in PWH than in people without. Some of the risk factors for COVID-19 severity—hypertension, diabetes mellitus, chronic obstructive pulmonary disease, renal disease and cancer—are also more common in PWH than in populations without HIV of similar age and sex. This presentation will summarize the state of the art and will highlight the importance of the choice of the groups against which COVID-19 outcomes in PWH are compared. Finally, it will also address that in order to establish the effect of HIV on SARS-CoV-2 susceptibility and COVID-19 severity, it is necessary to control for confounding variables that may be partly or fully responsible for the reported associations. It is also important to understand the role of comorbidities that are more common in PWH and may be the result of HIV infection.

**32 THE IMPACT OF COVID-19 ON THE HIV PANDEMIC WORLDWIDE**

**Andrew D. Kambugu**, *Makerere University, Kampala, Uganda*

With the emergence of the COVID-19, the loss of the hard-won momentum towards HIV epidemic control has become a major concern globally. The containment measures associated with COVID-19, including lockdowns, travel restrictions and physical distancing, which result in restricted access to essential services, compounded by the diversion of human and other key resources to address the pandemic, have led to significant disruptions in HIV service delivery and demand. During the earlier phase of the COVID-19 outbreak, modeling studies estimated a 10% increase in deaths among persons living with HIV in low- and middle-income countries (LMICs) as a result of the health systems disruptions occasioned by the pandemic, with interruptions in antiretroviral supplies being the key driver of mortality. Emerging data from multi-country surveys indicate that almost 1 in 7 countries have had either high or very high disruptions in HIV service delivery. Specifically, COVID-19 has resulted in substantial disruptions in HIV testing services, resulting in significant reductions in HIV case-identification and treatment initiation across many age groups. There is also emerging evidence of reductions in patient retention and viral suppression. This talk will focus on the impact of COVID-19 on the HIV pandemic worldwide. It will highlight the drivers of the disruptions to the HIV care system, from containment measures including lockdowns and other restrictions, the diversion of substantial resources to address COVID-19, the high demand on the health systems, to COVID-19 stigma and other human rights concerns. The data suggest that the most vulnerable communities are bearing the brunt of the COVID-19-induced health systems disruptions. The talk will summarize insights from local and regional modeling studies on the impact of COVID-19 on HIV health systems as well as share emerging data on the direct and indirect impacts on services delivery across different regions. Finally, the talk will highlight proposals for and documented approaches to mitigating the effect of COVID-19 on the HIV pandemic.

**33 THE IMPACT OF COVID-19 BEYOND HIV**

**Helen Bygrave**, *International AIDS Society, Geneva, Switzerland*

The impact of the COVID-19 pandemic spans across our health systems. Whilst mortality due to COVID-19 itself dominates headlines, it will only be upon reflection of all-cause mortality that the full impact of COVID on death will be known. Globally, 90% of countries surveyed by the World Health Organization (WHO) in 2020 experienced disruptions in health services, with the greatest disruptions being reported in low- and middle-income countries (LMICs). COVID-19 has exposed what those of us working in HIV have long understood – social inequities and weak health systems are only exacerbated by a health emergency. There is increasing acknowledgment that HIV services need to person-centred – and ensure integration of other essential health services, such as vaccination for HIV-exposed and HIV-infected infants, contraceptive care and services for other chronic non communicable diseases (NCDs). However, these services have been some of the most frequently disrupted during the pandemic. A study commissioned by UNICEF estimated that an additional 6,000 children could die every day from preventable causes as the COVID-19 pandemic continues to weaken health systems and disrupt routine services. Modeling estimates demonstrate that a 10% proportional decline in use of short- and

long-acting reversible contraceptive methods in LMICs would result in an additional 49 million women with an unmet need for modern contraceptives and an additional 15 million unintended pregnancies over the course of 1 year. Globally, those living with NCDs have an increased risk of severe disease if infected with COVID-19 but in over half of countries surveyed with community transmission of COVID-19, hypertension, diabetes, and cancer services were significantly disrupted. This presentation will present the global data on how health systems have been disrupted by the COVID-19 pandemic and, through the lens of vaccination, contraceptive care, and NCDs, describe not only the impacts, but how health services have responded and adapted. Learning from these adaptations, many of which have overcome long-term policy barriers, we must take the opportunity to build our health systems back better as we plan our recovery.

#### 34 FEAR AND COVID-19: EXPERIENCES ON THE GROUND

**Francois Venter**, *Ezintsha, Wits Reproductive Health & HIV Institute, Johannesburg, South Africa*

The impact on services and supply lines of the epidemic and various forms of lockdown is covered in preceding presentations. I will focus more on the personal impact of the COVID-19 pandemic on HIV-positive patients, families, and health workers. There is little research on social impacts, especially from resource-poor environments, so this relies somewhat on personal experience, colleague and patient anecdote, and (often fragmented) media reports, largely from the Southern African region. Reports from patients, and substantiated by informal donor monitoring, suggest large numbers of patients endured fear-driven antiretroviral interruptions, conservatively estimated at over a million patients (around 20%) in South Africa, possibly worse in countries with weaker supply systems. HIV testing, antiretroviral initiations, and male circumcision programmes ceased to operate for much of 2020. Fear was voiced by patients and families on several fronts: Many countries used iron-fisted security approaches (and used to quash political opposition, as happened in Uganda), with over 340 000 people arrested in South Africa in 2020 alone for lockdown offences, with footage of soldiers brutally forcing people off streets into crowded shacks. Many patients reported fear of being arrested while collecting their medication. Limited and crowded public transport, as well as distrust of clinic infection control measures, were cited for non-attendance. Foreigners were excluded in many programmes from supportive services (in South Africa, with many migrants, excluded foreigners from food parcels and unemployment insurance). Initial reports of exclusion of foreigners from vaccine programmes have been firmly reversed in South Africa, triggered by the recognition of rising vaccine nationalism in richer countries. The impact on health care workers has been widely reported in the media around the globe, spanning experiences of illness and death of colleagues triggering acute workforce shortages, to burnout and empathy fatigue. Shortages of protective equipment and labour demands for higher-than-necessary levels of equipment again speak to occupational fear reminiscent of HIV transmission concerns in the very early 80s. There is some evidence that health systems and health workers demonstrated remarkable increased resilience in subsequent "2nd waves" as experience with protections and increases in patient loads improved.

#### 36 HIV-1 bNAbs: LOOKING AHEAD

**Marina Caskey**, *The Rockefeller University, New York, NY, USA*

Combination antiretroviral therapy (ART) is highly successful in suppressing viral replication and preventing disease progression; however, it cannot eradicate HIV-1 infection. ART is also effective in preventing infection from sexual exposure, but efficacy is highly dependent on adherence to the regimen. Therefore, efforts to develop novel preventive and therapeutic interventions with a longer duration of action and to identify strategies that can eradicate or induce treatment-free long-term HIV-1 remission remain critical. Broadly neutralizing antibodies (bNAbs) may represent an alternative strategy to combat HIV-1 infection. Monoclonal antibodies, which are made in the laboratory but based upon natural human antibodies with high potency, are considered to be promising candidates for safe, long-acting agents for prevention or therapy. Importantly, bNAbs differ from ART in that they can recruit immune effector functions through their Fc domains to accelerate clearance of viruses and infected cells. In addition, immune complexes are potent immunogens that can foster development of host immune responses. These unique characteristics place bNAbs as promising candidates for HIV cure or remission strategies. In the past decade, a number of HIV-1 bNAbs have been

developed and are undergoing clinical evaluation. We will discuss results from both preclinical and clinical studies of anti-HIV-1 bNAbs and their potential role in HIV prevention, therapy, and cure strategies.

#### 37 SUSTAINED DELIVERY AND LONG-ACTING AGENTS FOR PREVENTION OF HIV

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

The approval, availability, and scale-up of oral preexposure prophylaxis (PrEP) for HIV continues to impact on population level HIV incidence around the world, shining a spotlight on the potential of primary prevention in ending the HIV epidemic. Yet, for many reasons daily oral PrEP is not and may never be feasible for every individual and every setting. Long-acting agents, long a key focus of research and development, are finally coming into their own and getting ready to offer PrEP consumers an expanded choice of options. This talk will provide an overview of the menu of long-acting agents becoming available, their efficacy and safety profiles, their advantages and limitations, and how we can prepare to mitigate challenges.

#### 38 HIV-1 AND SARS-CoV-2: DURABILITY OF HOST IMMUNE RESPONSES FROM VACCINATION OR INFECTION

This highly interactive session begins with a brief overview of the issue or controversy. The scientific experts each offer their opinions or observations in a 5-minute summary, followed by a 30-minute, spirited discussion among the panel members. The moderator will bring in comments and questions from the audience. This session will address the waning immunity in SARS-CoV-2 infected populations, T-Cell immunity in SARS-CoV-2, population-level immunity, programming durable immunity, and pathological B-cell activation during SARS-CoV-2 infection.

#### 39 FROM DAILY PILLS TO MONTHLY SHOTS FOR HIV PREVENTION AND TREATMENT: CAN EFFICACY BE TRANSLATED INTO EFFECTIVENESS?

This panel discussion will address the challenges of long-acting agents for HIV prevention and treatment at the clinic and population levels. The panel will present insights into the use of long-acting agents for treatment and prevention, the latest information on pharmacokinetic and drug resistance considerations with long-acting agents, and perspectives on implementation considerations from the US and global physicians.

#### 40 PrEP SCALE-UP TO MEET UNAIDS 2030 GOAL: IT JUST ISN'T POSSIBLE—OR IS IT?

This interactive discussion will highlight the challenges that need to be overcome to achieve the 2030 UNAIDS targets. Opportunities and challenges to meeting these goals via a singular focus on antiretroviral treatment for people with HIV (ie, absent biomedical prevention scale-up) or in partnership with biomedical prevention will be highlighted, using recent randomized clinical trial data on treatment as prevention (TasP) programs and recent programmatic accomplishments in pre-exposure prophylaxis (PrEP) scale-up as starting points for discussion.

#### 41 INTRINSIC RESISTANCE OF RESERVOIR CELLS TO IMMUNE KILLING

**R. Brad Jones**, *Weill Cornell Medicine, New York, NY, USA*

Cytotoxic T-cell (CTL) responses against HIV play a critical role in partially controlling viral replication in the absence of antiretroviral therapy (ART), but fail to eradicate HIV reservoirs. The ability of these reservoirs to persist on ART, despite CTL, is generally attributed to 3 primary factors: 1) viral latency – a barrier to detection by CTL 2) inadequate magnitudes or effector functions of CTL, and 3) sequestration of some components of the reservoir in anatomical sanctuaries that largely exclude CTL. Here, we present evidence, rationale, and mechanistic insights supporting the existence of a fourth element, arising from differences in the intrinsic sensitivities of target cells to elimination by CTL. Target cells play active roles in the process of CTL killing, through participation in the formation of immunological synapses, and by "deciding" whether or not to undergo apoptosis, based on the integration of complex signaling pathways (which include negative regulators, eg, Serpin B9, BCL-2). The HIV reservoir comprises populations of long-lived infected cells that can undergo clonal expansion. The properties of these cells, and their progeny, thus become a key factor in understanding and overcoming HIV persistence. We will summarize the evidence supporting that intrinsic resistance to CTL is a property of reservoir-harboring cells on long-term ART, which may have limited the efficacy of "kick and kill" strategies to date, as well as the role of the pro survival protein BCL-2

in this phenomenon, and opportunities to overcome this therapeutically. In addition to BCL-2, we will present an update on additional diverse mechanisms of CTL resistance emerging from transcriptional screens, and in vitro functional validation and investigation, presenting results derived from both CD4+ T-cell and macrophage targets. These results will be contextualized alongside the relatively well-developed understanding of mechanisms at play in certain types of cancer, where the clonal expansion of tumor cells enables selection for CTL-resistant clones. In emphasizing the role of reservoir-harboring CTL targets, not only as presenters of antigen, but also as active and self-regulating partners in the processes of cytolysis, we hope to highlight a rich source of potential therapeutic targets that may augment strategies aimed at depleting HIV reservoirs.

#### 42 HOW TO GENERATE GOOD KILLERS BY INITIATING ART (NOT TOO) EARLY?

**Lydie Trautmann**, *Oregon Health and Sciences University, Portland, OR, USA*  
HIV infection results in significant defects in immune cell functions, including the inability to kill HIV infected cells due to chronic antigen exposure and immunosuppressive mechanisms triggered by chronic infection and inflammation. These immune dysfunctions are incompletely resolved by ART, resulting in viral reservoir persistence that impedes efforts to achieve long-term HIV remission. Two main immune cell types exhibiting cytolytic activity are necessary to eliminate HIV-infected cells in the body: CD8 T cells and NK cells. However, HIV infection renders both CD8 and NK cells dysfunctional, even after long-term ART. Some mechanisms of dysfunction in these cells will be discussed, as well as the effect of latency reversing agents on the function of these cells. Since these cells play a critical role in limiting viral replication early in acute HIV/SIV infection, early initiation of ART has been hypothesized to help preserve their capacity to efficiently eliminate HIV infected cells. Very limited data are available on the effect of early treatment on NK cell function. For CD8 T cells, while early initiation of ART in the first weeks of infection leads to the generation of cells that proliferate more and are better killers than when ART is initiated in chronic infection. However, these cells are at lower numbers in individuals who initiated treatment early. New data from the NHP model show that CD8 T cells with preserved function after early ART initiation can help reduce the viral set point, but their response is still too late to control viral rebound after ART cessation. Therefore, early initiation of ART can generate good killers but the timing of expansion and differentiation of these cells is still a barrier for HIV control. In addition, very early ART initiation leads to even smaller numbers of HIV-specific CD8 T cells and prevents development of antibodies that promote NK cell-mediated antibody-dependent cellular cytotoxicity, suggesting that timing of ART initiation in acute infection is important. For people who have not been treated early enough, immune checkpoint blockers are being tested to determine if they are able correct the dysfunctions in killing as has been shown in cancer. The use of therapeutic vaccines and administration of genetically engineered cells are also being explored to boost these cytotoxic responses. These strategies aiming at boosting CD8 T cell and NK cell cytolytic functions and induce HIV remission will be presented.

#### 43 BREAKING THE B-CELL FOLLICLE BARRIER TO ELIMINATE VIRAL RESERVOIRS

**Afam Okoye**, *Oregon Health and Sciences University, Portland, OR, USA*  
Follicular helper T cells (TFH) are a specialized subset of CD4+ T cells that interact with antigen-specific B cells within specialized structures known as germinal centers in B cell follicles of secondary lymphoid tissues. This interaction is required for antibody affinity maturation and the differentiation of germinal center B cells into long-lived memory B cells and plasma cells. Migration into B-cell follicles is highly regulated by chemokine/chemokine receptor interactions, in particular CXCL13/CXCR5, providing for specific ingress of CXCR5+, CD4+ TFH and other minor populations of CXCR5+ regulatory T cells, but not other (CXCR5-) T cell types, including the vast majority of antiviral effector CD8+ T cells. CD4+ TFH are susceptible to HIV (and SIV) infection and can support active viral replication and production in vitro and in vivo. Untreated HIV/SIV infection leads to an accumulation of CD4+ TFH, which can contain relatively high proportions of HIV/SIV RNA+ cells. In SIV-infected monkeys, productive SIV infection becomes almost exclusively CD4+ TFH cell-restricted upon attainment of elite virologic control, suggesting that the highly effective antiviral CD8+ T-cell responses in SIV elite controllers were able to almost completely clear and/or suppress productive SIV infection in extra-follicular T-cell zones, but not

within B cell follicles. This is highly relevant for HIV cure because it implies even the most effective antiviral CD8+ T cell responses will be limited in their ability to destroy or suppress reactivating virus in CD4+ TFH both during ART and after ART cessation. This talk will discuss ongoing efforts to disrupt this "B-cell follicular sanctuary" to fully evaluate the ability of virus-specific CD8+ T-cells to achieve durable, post-ART virus remission.

#### 44 TYPE I INTERFERON RESISTANCE OF REBOUND HIV-1

**Beatrice H. Hahn**, *University of Pennsylvania, Philadelphia, PA, USA*  
Type 1 interferons (IFN-I) are potent innate antiviral effectors. However, harnessing these cytokines for HIV-1 prevention, treatment, and cure strategies has been hampered by an incomplete understanding of the role of endogenously produced IFN-I in viral control. To examine the kinetics of the IFN-I response over the course of HIV-1 infection, we generated 500 clonally-derived HIV-1 isolates from the plasma and CD4+ T cells of 26 individuals sampled prospectively before and after antiretroviral therapy (ART), and/or during analytical treatment interruption (ATI). Determining the concentration of IFN $\alpha$ 2 and IFN $\beta$  that reduced viral replication in vitro by 50% (IC<sub>50</sub>), we found consistent changes in the sensitivity of HIV-1 to IFN-I inhibition both across individuals and over time. IFN-I resistance was uniformly high during acute infection, decreased in all individuals in the first year post-infection, was reacquired concomitant with CD4+ T cell loss, and remained elevated in individuals with accelerated disease. Isolates obtained by viral outgrowth during suppressive ART were relatively IFN-I sensitive, resembling viruses circulating just prior to ART initiation. However, viruses that rebounded following treatment interruption displayed the highest degree of IFN $\alpha$ 2 and IFN $\beta$  resistance observed at any time during the infection course. Interestingly, IFN $\alpha$ 2 IC<sub>50</sub> values of rebound isolates from individuals treated with pegylated IFN $\alpha$ 2 before and during ART interruption were on average 1.8-fold higher than those of rebound isolates from IFN $\alpha$ 2 untreated individuals, and such differences were not observed for the corresponding IFN $\beta$  IC<sub>50</sub> values. IFN-I-resistant viruses did not share a particular biological phenotype, but some rebound viruses were exquisitely macrophage tropic. Finally, an analysis of post-ATI isolates generated by viral outgrowth suggested that treatment interruption may have re-seeded the reservoir with IFN-I resistant viruses in some patients. These findings indicate a dynamic interplay between host innate immune responses and the evolving HIV-1 quasispecies, with the relative contribution of IFN-I to HIV-1 control impacted by both ART and analytical treatment interruption. Although elevated at transmission, host innate pressures are the highest during viral rebound, limiting the viruses that successfully reactivate from latency to those that are IFN-I resistant.

#### 45 TRIPLE DRUG ART, DUAL ART, OR JUST ART?

**Jose R. Arribas**, *Hospital La Paz Institute for Health Research, Madrid, Spain*  
Over the last 2 years, for the first time in the history of modern antiretroviral therapy (ART), expert guidelines (EACS, DHHS, IAS-USA) have started to include 2-drug ART regimens as recommended combinations for most people with HIV (PWH), both as initial and as maintenance therapy in the setting of virological suppression. Currently 2-drug ART can be administered orally and very soon it would be available for prescription as long-acting formulations. This advance has been possible because of the advent of second-generation integrase strand transfer inhibitors with a genetic barrier so high they require only 1 reverse transcriptase inhibitor to complete an effective ART regimen. In this presentation I will review the efficacy and safety data supporting the use of two-drug oral ART in ART-naïve and virologically suppressed PWH and of long-acting two-drug ART in virologically suppressed PWH. I will also discuss current gaps of knowledge and the pros and cons of using 2- versus 3-drug ART regimens. I will also review scenarios that are more suitable for two-drug ART, in both oral and long-acting forms.

#### 46 NOVEL ANTIRETROVIRAL THERAPIES IN CLINICAL DEVELOPMENT

**Alexandra L. Calmy**, *University Hospitals of Geneva, Geneva, Switzerland*  
Innovative drugs in the development pipeline for HIV treatment are at a crossroads. The model of introducing drugs with incremental improvements within existing drug classes is now fading. Drugs aimed at novel targets may have a greater impact, especially for providing new options in individuals multi-exposed to ARVs. The scientific community has moved research into combined strategies aiming at long-acting molecules developed with multifaceted objectives way beyond the sole control of viral suppression. Novel HIV drugs and

combinations are being developed for prevention, treatment, and/or attacking the reservoirs of latent HIV. Continuous investment in novel HIV treatment strategies should be ensured, despite competing priorities, in order to improve the quality of life of affected individuals and to achieve the goal of epidemic control. Public health improvement strategies will require that early on in the development of drugs, diversity is represented at all stages of clinical research.

**47 ARVS AND ART FOR NEWBORNS AND INFANTS: A LAST FRONTIER**

**Moherndran Archary**, *University of KwaZulu-Natal, Durban, South Africa*

This state-of-the-ART talk on antiretroviral drugs and antiretroviral treatment in neonates and infants will focus on: 1) the considerations when evaluating the safety and dosing of new ARVs in infants and young children, 2) the additional considerations when treating premature infants with antiretroviral drugs for prophylaxis or treatment, 3) the evolving paradigm around the use of antiretroviral drugs for prevention and treatment of HIV during the newborn period, 4) the role of transplacental transfer of antiretroviral drugs in loading the neonate in the peripartum period, 5) discussion on currently available antiretroviral drugs used to treat neonates/infants, and 6) discussion on antiretroviral drugs and delivery systems that are in the pipeline for prevention and treatment of HIV across the pediatric age range.

**48 GOT ANYTHING FOR THIS COUGH? NEW ANTIVIRALS FOR TREATMENT OF SARS-CoV-2**

**Davey M. Smith**, *University of California San Diego, La Jolla, CA, USA*

Attendees to this presentation will be introduced to currently available and promising antiviral agents for SARS-CoV-2. These agents will include monoclonal and polyclonal antibodies, protease inhibitors, interferon-based agents, and small molecule drugs. The presentation will also touch on how viral variants of concern may impact the activity of some of these agents.

**49 SINGLE VASCULAR CELL HETEROGENEITY IN HEALTH AND DISEASE: A COVID-19 UPDATE**

**Peter Carmeliet**, *University Hospitals Leuven, Leuven, Belgium*

On the basis of emerging evidence from patients with coronavirus disease 2019 (COVID-19), we postulate that endothelial cells are essential contributors to the initiation and propagation of severe COVID-19. COVID-19, caused by the betacoronavirus SARS-CoV-2, is a worldwide challenge for health care systems. The leading cause of mortality in patients with COVID-19 is hypoxic respiratory failure from acute respiratory distress syndrome (ARDS). To date, pulmonary endothelial cells (ECs) have been largely overlooked as a therapeutic target in COVID-19, yet emerging evidence suggests that these cells contribute to the initiation and propagation of ARDS by altering vessel barrier integrity, promoting a procoagulative state, inducing vascular inflammation (endotheliitis) and mediating inflammatory cell infiltration. Therefore, a better mechanistic understanding of the vasculature is of utmost importance. Here, we discuss current insights into endothelial cell biology in health and disease focusing on their heterogeneity between and within vascular beds, the divergent global and metabolic characteristics they display and that correlate with the specific functions of the particular endothelial cell subtypes, and discuss the link between endothelial cells, viral infection, and inflammatory changes, proposing novel therapeutic strategies.

**50 BODY ON FIRE: MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN**

**Elizabeth A. Whittaker**, *Imperial College London, London, UK*

In April 2020, reports of an inflammatory condition with overlapping features of Kawasaki disease and toxic shock syndrome emerged in Italy and the UK, and subsequently other countries in Europe, the Americas, and Asia have reported cases of this rare syndrome, now called Paediatric Inflammatory Multisystem Syndrome (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C), that is temporally associated with SARS-CoV-2 infection. Case definitions use criteria including clinical manifestations (fever, inflammation, organ dysfunction), elevated biochemical markers of inflammation, and evidence of contact or infection with SARS-CoV-2, with exclusion of another microbial cause. There are many questions currently emerging that need to be answered—for example, how the pathophysiology of MIS-C differs from other paediatric conditions such as Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome. Does the immunology differ from that of severe COVID-19 disease in adults? What are the optimal treatment regimens? Can we improve diagnosis, and hence early recognition and outcomes? In this

talk, I will outline the epidemiology, clinical presentation and management, as well as our current understanding of this emerging inflammatory condition.

**51 THINK ABOUT IT: NEUROLOGIC MANIFESTATIONS OF COVID-19**

**Benedict D. Michael**, *University of Liverpool, Liverpool, UK*

In this presentation, Dr Michael will review the results of the clinicoepidemiologic studies of the neurological and neuropsychiatric complications associated with COVID-19, their implications for clinical practice, and insights from on-going studies of underlying disease mechanisms.

**52 COVID-19: CONCERNS OF THE HEART**

**Valentina O. Puntmann**, *Goethe University, Frankfurt, Germany*

Cardiac involvement due to COVID-19 infection is an increasingly recognized complication. In this talk, Dr Puntmann will provide an overview of the current state of the knowledge. She will address some of the controversies in terms of the diagnostic choices in detecting cardiac inflammation. She will also share the insights from the Frankfurt Cohort, the largest prospective study of patients with recent COVID-19 infection and serial follow-ups with cardiovascular magnetic resonance.

**53 YOUNG WOMEN: ADHERENCE, EFFECT, AND RETENTION**

**Thesla Palanee-Phillips**, *Wits Reproductive Health and HIV Institute, Johannesburg, South Africa*

Biomedical HIV prevention strategies such as preexposure prophylaxis (PrEP) are designed to maximize public health impact at a population level. Despite current HIV prevention and treatment tools having helped reduce incident HIV infections and AIDS-related deaths in the last decade, urgency remains around the need to identify additional options. Meeting global HIV reduction targets will require improved service-delivery platforms to get prevention choices to people at risk at an individual level while layering prevention coverage to achieve population-level impact. HIV prevention programmes usually focus on prevention of HIV through a complementary combination of behavioural, biomedical and structural strategies. Scientific evidence of oral PrEP efficacy as a strong HIV prevention tool has gained strength from data from demonstration projects. Daily oral PrEP is currently the only available prevention product for women with regulatory approval, other than condoms, although the monthly dapivirine vaginal ring (DVR) received a positive scientific opinion from the European Medicines Agency (EMA) in July 2020 and a WHO recommendation in January 2021, and may become available in some countries soon. Despite increasing availability of oral PrEP and the anticipated future availability of the DVR option, both products have demonstrated varying levels of effectiveness in young women. Low adherence has contributed to a lack of efficacy in clinical trials and, coupled with high rates of PrEP discontinuations observed in clinical practice, threatens their public health impact. These outcomes support pursuit of a multi-pronged approach: continued and development of highly effective, affordable, discrete HIV prevention interventions that are acceptable to end-users while ensuring higher levels of protection, all while intensifying efforts to better understand barriers and facilitators to oral and topical PrEP initiation, execution and persistence for protection. If strategies to circumvent known barriers to adherence to PrEP use can be identified and implemented, more effective use of current as well as future PrEP options may be assured through their extension. This presentation will focus on understanding challenges related to adherence, retention, and their impact on PrEP efficacy among women and explore mechanisms to strengthen the HIV prevention toolbox arsenal.

**54 CHALLENGES AND OPPORTUNITIES IN IMPLEMENTING PrEP IN KEY POPULATIONS**

**Gregorio A. Millett**, *amfAR, New York, NY, USA*

Greg Millett will discuss PrEP in key populations, including men who have sex with men, transgender individuals, sex workers, incarcerated populations, and refugees. His talk will focus on implementation issues on the ground in key populations across the planet, highlighting both challenges and models of success.

**55 MODELS OF DELIVERING PrEP IN EAST AFRICA: INNOVATIONS AND LESSONS LEARNED**

**Moses R. Kanya**, *Makerere University College of Health Sciences, Kampala, Uganda*

Oral pre-exposure prophylaxis (PrEP) is highly effective and could bring us closer to HIV elimination targets if offered alongside testing and treatment.

However, this effective HIV prevention intervention is only beginning to be scaled up in many settings globally. A number of demonstration projects and implementation research studies have been conducted in East Africa among populations with increased potential for HIV exposure. Implementation experiences are beginning to emerge, including high levels of interest in and willingness to use PrEP, but modest rates of persistence in some settings. In this presentation, we will discuss lessons learned regarding PrEP delivery from the first generation of demonstration and implementation studies in East Africa. We will explore models of facility and community-based PrEP delivery, associated PrEP uptake, use, and implementation experiences, both among subpopulations and the general population. We will also discuss future innovations in PrEP delivery, including strategies for achieving lower-barrier access and simplifying PrEP delivery. The implications of these findings for delivery approaches for oral PrEP and future long-acting prevention modalities will be highlighted.

**56 INCORPORATING INJECTABLE PrEP AND NEWER FORMULATIONS INTO LMIC**

**Yogan Pillay**, *Clinton Health Access Initiative, Pretoria, South Africa*

Dr Pillay will discuss perspectives about the rationale and considerations for long-acting PrEP as an additional HIV prevention tool for low and middle income countries, in addition to anticipating and preparing for implementation issues.

**57 ELITE CONTROLLERS: A MODEL FOR A FUNCTIONAL CURE OF HIV-1 INFECTION**

**Xu Yu**, *Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*

HIV integrates into the host genome to establish life-long infection, requiring indefinite antiretroviral therapy. The development of novel strategies that induce a long-term, drug-free remission of HIV-1 infection has evolved as one of the highest-priority objectives for the HIV research community. Intriguingly, such a long-term, drug-free remission or "functional cure" of HIV-1 infection is naturally observed in a small number of HIV-1-infected individuals, termed "elite controllers (ECs)", who maintain undetectable levels of HIV-1 replication and do not show clinical evidence of HIV-1 disease progression. Recent advances in technology development allowed us to comprehensively profile the proviral landscape within HIV-1 reservoir cells in people living with HIV. Near full-length individual proviral sequencing (FLIP-Seq) and matched integration site analysis (MIP-Seq) revealed that replication-competent intact proviruses accumulated in non-genic or heterochromatin regions of the human chromosomes in ECs. In extremely rare cases, intact proviruses were undetectable despite analyzing massive numbers of cells, suggesting a sterilizing cure of HIV-1 infection might have been achieved in these exceptional elite controllers. In addition, single-cell assays able to simultaneously capture the proviral sequences, the corresponding chromosomal integration sites, and HIV RNA transcriptional activities in unmanipulated patient-derived cells have recently been developed. This multidimensional analysis platform demonstrated that proviruses integrated into non-genic or heterochromatin regions of the human chromosomes had limited transcriptional activities and were in deep latency. Novel epigenomic profiling technologies will provide additional insights into the rebound-competent reservoirs. Assays that evaluate the qualitative, rather than quantitative, features of viral reservoir cells will be helpful for investigating the efficacy of clinical interventions aiming at a functional cure of HIV-1 infection.

**58 HIV TREATMENT IN PREGNANCY: BEYOND PREVENTION OF VERTICAL TRANSMISSION**

**Shahin Lockman**, *Brigham and Women's Hospital, Boston, MA, USA*

Women comprise more than half of persons living with HIV globally, and most women with HIV will be pregnant at least once. It is essential to understand the impact of HIV treatment during pregnancy on not just vertical transmission but also on obstetric and maternal and child health outcomes, in order to optimize the health of women and children through their life course. The global scale-up of antiretroviral treatment (ART) over the past 10 years has resulted in a continued decline in new pediatric HIV infections (although challenges remain). The past decade has also offered an increased understanding that the antiretroviral regimen in pregnancy can affect health outcomes other than vertical transmission, and that adverse outcomes associated with antiretrovirals in pregnancy can disrupt global ART programs, particularly for women. These realizations have led to an appreciation of the importance of timely and robust data on the safety and expected efficacy of HIV drugs used in pregnancy and during lactation. This talk will briefly touch upon the prevention

of vertical transmission and will then review major findings regarding the relationship between maternal ART regimens in pregnancy, and pregnancy outcomes and maternal and child health outcomes. Current recommendations for antiretroviral use in pregnancy and lactation will be summarized. Important evidence gaps will be highlighted, and potential approaches for addressing these gaps through more timely research in pregnancy will be discussed.

**59 SARS-CoV-2 AND THE HOST IMMUNE RESPONSE: GOOD VS BAD IMMUNITY**

This highly interactive session begins with a brief overview of the issue or controversy. The scientific experts each offer their opinions or observations in a 5-minute summary, followed by a 30-minute, spirited discussion among the panel members. The moderator will bring in comments and questions from the audience. This session will address several aspects of immunity directed to SARS-CoV-2, including innate, humoral, and cellular immune responses.

**60 COVID-19 CLINICAL CONTROVERSIES**

Based on illustrative case vignettes, a panel of experts will have a moderated and lively exchange of what they consider to be optimal treatment strategies and what issues require our attention in terms of potential long-term health concerns once patients recover from the acute episode of illness.

**61 COVID-19 DISPARITIES: HOW CAN THEY HELP MOVE THE NEEDLE FORWARD?**

This session will summarize critical data on the SARS-CoV-2 pandemic among several populations that experience disproportionate burdens of morbidity and mortality due to COVID-19. Speakers will also give recommendations for key interventions that could substantially decrease these disparities and participate in an interactive panel discussion with audience participation.

**62 NOVEL FINDINGS OF NEURONAL MODULATION OF HIV EXPRESSION IN MICROGLIA**

**Jonathan Karn**, *Case Western Reserve University, Cleveland, OH, USA*

Although cART dramatically lowers the levels of viral RNA in the brain, it does not reduce the incidence of HIV-associated neurocognitive disorders (HAND), which still develop in up to 50% of persons with HIV. Initial studies indicated paradoxically that the development of HAND correlates strongly with systemic inflammation and CNS inflammation, but did not correlate with the number of HIV-infected cells or viral antigens in the CNS. HIV latency was studied in a wide variety of systems, including immortalized human microglial cells, in iPSC-derived microglial cells, in brain organoids modified to incorporate microglial cells, and finally, in humanized mice. Pathways regulating HIV transcription were studied by co-culture experiments, drug treatments, and ex vivo induction of HIV in latently infected cells. The identities and polarization states of the cells were demonstrated by single-cell RNA-seq studies. Entry of HIV into latency is in response to specific repressive signaling pathways, especially due to signals emanating from healthy neurons in co-culture experiments with iPSC-derived neurons and in brain organoids. Although the mechanism underlying the neuronal silencing of HIV infections is not yet fully understood, key mediators of HIV silencing include the glucocorticoid (GR/NR3C1), Nurr1 (NR4A), and retinoid X (RXR) receptors, which can potentially be targeted by therapeutic drugs to prevent HIV reactivation. By contrast, reactivation of latent HIV occurs in response to inflammatory signals such as IL-1 $\beta$ , TNF- $\alpha$  or TLR agonists—all signals correlating with the severity of HAND. Humanized mice models developed by the Cannon and Karn laboratories show that human microglia recovered from the brains of the mice are indistinguishable from primary human microglia by surface markers and by single-cell RNA-Seq (scRNA-Seq) analyses. We have combined these analyses with our highly sensitive next-generation sequencing assay for HIV transcripts, the EDITS assay, and demonstrated that human microglia isolated from HIV-infected mice carry latent HIV proviruses that can be reactivated ex vivo by TNF- $\alpha$  and poly (I:C). In vivo and ex vivo has demonstrated the linkage between inflammation and latent HIV infection of microglial cells. Building on detailed studies of the molecular mechanisms underlying HIV latency in microglial cells, we expect to identify and evaluate candidate therapies that interfere with these circuits and could serve as potential treatments for HAND.

### 63 **ROLE OF CNS CD4 T CELLS AND MACROPHAGES IN SIV NEUROPATHOGENESIS AND RESERVOIRS**

**Vanessa Hirsch**, *National Institutes of Health, Bethesda, MD, USA*

While the use of combination antiretroviral therapy effectively suppresses systemic viral replication, neurocognitive disorders remain a persistent clinical problem. Therefore, the use non-human primate models are necessary to study mechanisms of neuropathogenesis. Simian immunodeficiency virus (SIV)-infected non-human primates can serve as a relevant model for AIDS neuropathogenesis. The current SIV-induced encephalitis (SIVE)/neuroAIDS models are generally associated with rapid progression to neuroAIDS, which does not reflect the tempo of neuroAIDS progression in humans. In a recent study, we isolated a neuropathogenic clone SIVsm804E-CL757 (CL757) from an SIV-infected rhesus macaque. This virus causes more protracted progression to disease (approximately 1 year post-infection) and induces SIVE in 50% of inoculated animals, with high cerebral spinal fluid viral loads, multinucleated giant cells (MNGC), glial nodules, and perivascular lymphocytic cuffing in the central nervous system (CNS). This latter finding is reminiscent of HIV encephalitis in humans but is not generally observed in rapid progressor animals with neuroAIDS. By isolating mononuclear cells from the brains of SIV-infected rhesus macaques with and without encephalitis, we show that immune cells invade the neuroparenchyma and increase in number in the CNS in animals with SIV-induced encephalitis (SIVE). Recently we studied which subsets of cells within the CNS were targeted by CL757 in animals with neurological symptoms. Immunohistochemistry of brain sections from these animals demonstrated infiltration of CD4+ T cells and macrophages to the site of MNGCs. Moreover, an increase in mononuclear cells isolated from the brain tissues of rhesus macaques (RM) with SIVE correlated with increased CSF viral load. Subset analysis showed a specific increase in brain CD4+ memory T cells (Br-mCD4), brain-macrophages, and Br-B cells. Both Br-mCD4s and Br-macrophages harbored replication-competent viral DNA as demonstrated by virus isolation by co-culture. However, only in animals exhibiting SIVE/neuroAIDS was virus isolated from Br-macrophages. These findings support the use of CL757 to study the pathogenesis of AIDS viruses in the central nervous system and indicate a previously unanticipated role of CD4s cells as a potential reservoir in the brain that might persist during antiretroviral therapy.

### 64 **MYELOID CNS HIV RESERVOIRS...THE DEBATE CONTINUES**

**Lishomwa Ndhlovu**, *Weill Cornell Medicine, New York, NY, USA*

Gallant efforts are ongoing to achieve sustained antiretroviral therapy (ART)-free HIV remission. With the exception of two stem-cell transplantation cases and the few instances of natural control, this has been proven challenging. Recent advances have highlighted the importance of myeloid reservoirs as sanctuaries of HIV persistence and therefore may partially be responsible for viral recrudescence following analytical antiretroviral treatment interruption. The ongoing debate in the field as to whether the central nervous system (CNS), encompassing the brain, spinal cord, and its cellular bodies, including myeloid cells, continues as to their contribution as sites of HIV persistence of latent replication or non-replication competent virus in the setting of ART. Further, most current human HIV cure-targeted clinical studies have primarily focused these efforts on targeting viral persistence in CD4 T cells in blood and tissue sanctuaries, and the lack of myeloid-centered HIV clinical trials focused on the CNS reservoir, either as primary or secondary end points, has hindered our understanding of the contribution of myeloid cells and the CNS as viral sanctuaries of rebound virus and may guide successes in future HIV eradication strategies. This presentation will highlight controversies, boundaries to overcome and new research efforts defining myeloid reservoirs and HIV persistence in the CNS and recent advances in HIV remission and cure trials that would be relevant in targeting this compartment, and make an argument as to their clinical relevancy as we progress towards sustained ART-free HIV remission in all people with HIV.

### 65 **LESSONS FROM CNS HIV ESCAPE AND ATI FOR UNDERSTANDING HIV PERSISTENCE IN THE CNS**

**Sarah B. Joseph**, *University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Direct sampling of putative HIV-1 reservoirs in the brain parenchyma of participants on antiretroviral therapy (ART) is typically impossible, making cerebrospinal fluid (CSF) the only material available for querying reservoirs in the CNS of living participants. CSF collected from people on ART generally contains extremely low levels of HIV-1 RNA and CD4+ T cells. In contrast,

elevated levels of HIV-1 RNA are observed in CSF collected from participants during CSF escape and treatment interruption (TI). Thus raising questions as to whether viral populations found in the CSF during CSF escape and/or TI represent virus production from reservoirs in the CNS or periphery. There is now sufficiently genetic and phenotypic data to indicate that HIV-1 populations in the CSF during CSF escape and TI have heterogenous origins with some emerging from myeloid reservoirs in the CNS and others arising from T cell reservoirs in the CNS and/or periphery. Cumulatively these results indicate that long-lived reservoirs can persist in CNS resident cells (i.e. microglia/macrophage), but the frequency of such reservoirs and their ability to generate viral recrudescence remains unknown.

### 66 **PrEP DURING PREGNANCY AND BREASTFEEDING**

**John Kinuthia**, *University of Nairobi, Nairobi, Kenya*

High HIV incidence among pregnant and breastfeeding women in sub-Saharan Africa highlights the critical need for primary prevention efforts. Pre-exposure prophylaxis (PrEP) is an effective woman-controlled HIV prevention strategy that is safe for mother and infants. In 2017, Kenya rolled out PrEP implementation for individuals at substantial risk of HIV including pregnant and breastfeeding women. Maternal and child health (MCH) clinics provide an effective platform for PrEP delivery and are less stigmatized locations for women to access HIV preventive interventions. The PrEP Implementation for Young Women and Adolescents (PrYA) program was implemented in 16 facilities in Kisumu County, western Kenya in collaboration with the Kisumu County Department of Health and the National AIDS and STI control program to deliver PrEP to women particularly adolescent girls and young women attending MCH clinics in a high HIV prevalence region in Kenya. This talk will discuss lessons learnt implementing the PrYA program including engagement with county and national government institutions, how PrEP was offered in MCH clinics, who took PrEP, reasons for initiating PrEP, reasons for not initiating PrEP among women with risk factors, and factors contributing to PrEP continuation.

### 67 **PrEP ADHERENCE INTERVENTIONS FOR ADOLESCENTS AND YOUNG ADULTS**

**Sybil Hosek**, *Stroger Hospital, Chicago, IL, USA*

Oral pre-exposure prophylaxis (PrEP) is a remarkably effective means of HIV prevention when taken consistently. Young African women and young men who have sex with men (MSM) in the US have demonstrated lower levels of PrEP adherence than older adults across multiple open label trials and demonstration projects. Given the biological, behavioral, and social developmental factors that influence adherence among adolescents, it is critical to identify evidence-based adherence support interventions for PrEP use. Strategies are needed to optimize PrEP adherence among youth, particularly for a prevention behavior that requires repetition on a daily basis, such as oral PrEP use. This presentation will review key interventions that have shown success at improving PrEP adherence among adolescents as well as interventions currently being tested that may prove promising in the future.

### 68 **IMPROVING ADOLESCENT PrEP USE: UNDERSTANDING DEVELOPMENTAL PROCESSES AND CONTEXT**

**Claude A. Mellins**, *New York State Psychiatric Institute, New York, NY, USA*

Ending the global HIV epidemic will be stymied without concerted efforts focused on adolescents, who represented nearly 25% of all new HIV infections in 2019. PrEP has revolutionized adult prevention efforts, and its safety and acceptability has resulted in authorization for adolescents in the US since 2018, with increasing use globally. Yet, data to date suggest adolescent uptake and persistent adherence to PrEP, similar to treatment of HIV and other health conditions, is a challenge. The goal of this talk is to further understanding of the context and developmental processes that drive these challenges in order to help providers work more effectively with adolescents and inform interventions to improve PrEP uptake and adherence. Adolescence is marked by profound changes in physical, social, cognitive and emotional function that impact health behaviors. Adolescents are developing gender and sexual identities, adjusting to developmental tasks important to adult transition (e.g., greater independence from parents, decision-making autonomy, peer affiliations, community engagement), and initiating intimate relationships. Imaging studies have identified central nervous system changes through age 25 years that impact maturation of emotion regulation, cognition,

problem-solving and decision-making skills. Although studies have focused on adolescence as a risky stage – associated with impulsivity, sensation-seeking, underdeveloped executive function, emotion dysregulation, experimentation with substance use and sexual behavior, and psychiatric disorders – for those at risk – adolescence also provides a critical period for developing lifelong healthy behaviors. The adolescent brain is designed for flexibility, tolerance of ambiguity, and targeted risk-taking and sensation-seeking – all key to adult transition. To optimize adolescent PrEP interventions, we advocate for (a) an appreciation of the neuro-cognitive, emotional, and social strengths of this stage and (b) consideration of the multiple factors that foster or protect against behavioral health risks relevant to PrEP use (e.g., cognition, mental health; substance use; family, peer and provider relationships; HIV stigma; health care, cultural context). A more holistic and strengths-based approach to examining adolescent decision-making in the context of development, life circumstance, and future aspirations may lead to more innovative methods for promoting engagement in and persistent adherence to PrEP.

#### 69 IMPROVING HOW WE MARKET PrEP TO YOUTH

**Elzette Rousseau**, *University of Cape Town, Cape Town, South Africa*

The benefits of pre-exposure prophylaxis (PrEP) for HIV prevention are well-established, however efficacy in high-incidence locations will depend on whether young people can effectively access, use, and adhere to PrEP. Demand creation in acceptable spaces and with positive messaging not just about the benefits of PrEP but also about how PrEP can conveniently fit into young people's lives are critical in motivating uptake and continued use. Young people, especially adolescent girls and young women (AGYW) in Africa, want 'fast-PrEP'. This presentation will cover modalities of differentiated PrEP delivery convenient for young people as well as how to attract target population to these services. In addition, innovations (including mobile health) will be discussed as a way to engage young people, assist them in deciding if PrEP is for them, mitigate unintentional PrEP interruptions and facilitate prevention-effective adherence.

#### 70 HEPATITIS C ELIMINATION: WHAT'S TAKING SO LONG?

**Annie Luetkemeyer**, *University of California San Francisco, San Francisco, CA, USA*

This talk will review current the status of the hepatitis C virus (HCV) epidemic in the US and globally, focusing on progress and impediments to meeting elimination goals. Dr Luetkemeyer will review models of successful widespread treatment and micro-elimination and strategies to address remaining barriers to elimination, including lessons learned from COVID-19 and approaches to highly impacted populations.

#### 71 MECHANISMS AND TREATMENTS OF STEATOSIS IN HIV

**Steven Grinspoon**, *Harvard Medical School, Boston, MA, USA*

Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of disease, progressing from simple steatosis, through mixed steatosis and lobular inflammation, to nonalcoholic steatohepatitis (NASH), and ultimately advancing to more advanced fibrosis, cirrhosis, and end-stage liver disease. NAFLD is a manifestation of metabolic disease, associated with obesity, visceral adiposity, and insulin resistance, and contributes to an increased risk for cardiovascular disease. Increased flux to the liver of substrate, including fatty acids, increased intra-hepatic de novo lipogenesis and reduced hepatic fat oxidation, are major mechanistic factors. NAFLD is an increasing cause of liver transplants. Among people with HIV (PWH), specific pathogenic factors may relate to increased weight and hepatic toxicities, particularly with specific antiretrovirals, including integrase strand transfer inhibitors (INSTIs). In addition, PWH, may experience increased visceral adiposity, proinflammatory stimuli, immune activation, insulin resistance and stimulation of critical hepatic metabolic pathways by viral envelope proteins. The prevalence of NAFLD is high, estimated at 35%, and the phenotype exaggerated among PWH. For example, NAFLD is seen at a lower BMI in association with a higher prevalence of NASH in PWH. FDA approval for drugs in this class requires resolution of NASH without increasing fibrosis or vice versa. No drugs have yet to be approved for this indication in the general population, though many are now under investigation. Among PWH, a limited number of trials have been performed, but data do show some promising potential strategies. Therapeutic strategies that target steatosis, may work by reducing insulin resistance, (eg, GLP-1 agonists and/or targeting de novo lipogenesis and hepatic fat oxidation [GHRH agonists]), or improving hepatic inflammatory, immune and fibrotic pathways (CCR2/5 antagonists). In addition,

specific agents are being tested for effects on adipogenic/lipolytic pathways (PPAR gamma agonists, steroyl CO-A Desaturase Inhibitors), antifibrotic and anti-inflammatory properties. Overall, significant efforts are being made to develop successful strategies for NAFLD/NASH in PWH.

#### 72 HARNESSING IMMUNITY TO CURE HBV

**Ulrike Protzer**, *Technical University of Munich, Munich, Germany*

Currently, there is no curative treatment for hepatitis B virus (HBV) infection. Available antivirals control replication and mitigate inflammation but -as in HIV infection- cannot attack the nuclear persistence form of the virus. Virus-specific immunity can eliminate and control HBV, but antibody, as well as T-cell responses, are barely detectable in chronic infection. Activating HBV-specific immunity may therefore be the clue to achieve HBV cure.

#### 73 NEW PROSPECTS FOR THE TREATMENT OF HBV

**Heiner Wedemeyer**, *Medizinische Hochschule Hannover, Hannover, Germany*

In this presentation, Heiner Wedemeyer will address new drug developments for hepatitis B management and cure. He will describe strategies that utilize current therapies to harness the immune response, discuss novel agents in the pipeline, and review how to best utilize these novel therapies in order to achieve functional cure with defined treatment endpoints in patients with chronic hepatitis B.

#### 74 LESSONS LEARNED AND CHALLENGES IN COVID-19 VACCINE TRIALS

**Kathleen Neuzil**, *University of Maryland, Baltimore, MD, USA*

In 2020, the development of SARS-CoV-2 vaccines proceeded at a historic pace. Facing many challenges early on - a new disease poorly understood immunity, and an uncertain trajectory of the outbreak - a U.S. government effort brought together many partners to develop and advance several SARS-CoV2 vaccines. The vaccine development model included harmonized trial designs, collaborating clinical trial networks, and collaborating laboratory and statistical efforts. As of February 2021, two mRNA vaccines are being distributed under FDA Emergency Use Authorization (EUA) and several other vaccines are in various stages of clinical testing. Properly interpreting and comparing estimates of efficacy in these trials requires an understanding of the many variables involved and their potential effect on efficacy estimates. This talk will review the framework for the U.S. Covid-19 trials and discuss challenges and lessons learned.

#### 75 EQUITABLE ROLL-OUT OF COVID-19 VACCINES IN THE UNITED STATES

**Michelle Williams**, *Harvard TH Chan School of Public Health, Boston, MA, USA*

The United States is experiencing an intense reckoning with structural racism, in part because of the disparate health effects of COVID-19 on racial minorities suffering from higher rates of infection, hospitalization, and death. Yet despite equity efforts, we are already seeing racial disparities in vaccine distribution across the country. Going forward, vaccination efforts should prioritize economically worse-off racial minorities, not only to mitigate the disproportionate impacts of the pandemic, but also to help alleviate the country's racial health disparities at large.

#### 76 VACCINE ACCEPTANCE

**Saad Omer**, *Yale University, New Haven, CT, USA*

Vaccine acceptance is a complex phenomenon that lies on a continuum with those who actively seek vaccination on one end and those who refuse all vaccines on the other. When we talk about vaccine hesitancy, we mean those who accept some, delay some, or refuse some vaccines. Where one lies on this continuum is the result of an interaction between many different individual factors, such as values, cognitive biases, and trust, as well as environmental factors, like social norms, affordability, and convenience. There are different approaches to reducing vaccine hesitancy, some of which rely on taking advantage of cognitive biases, and others that use social norms, moral inclinations, and trust. This presentation will explore how we can use these different approaches to increase vaccine uptake.

#### 77 GLOBAL DISTRIBUTION OF THE SARS-CoV-2 VACCINE

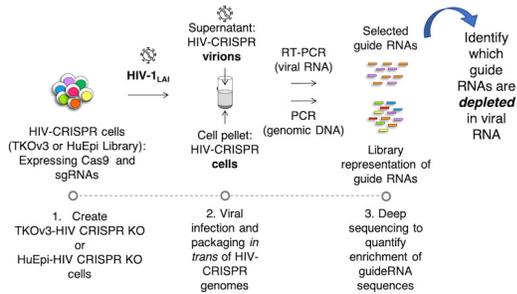
**Nicole Lurie**, *Coalition for Epidemic Preparedness Innovations, Washington, DC, USA*

This talk will describe the efforts of COVAX, a coalition of CEPI, Gavi and WHO, to develop, procure, and distribute SARS-CoV-2 vaccines for the world, with the goal of ensuring equitable access to those vaccines.

- 78 DECIPHERING THE HOST NUCLEUS SUBVERSION BY HIV-1 TO REPLICATE**  
**Viviana Scoca**<sup>1</sup>, Marion Louveau<sup>1</sup>, Renaud Morin<sup>1</sup>, Dmitry Ershov<sup>1</sup>, Jean-Yves Tinevez<sup>1</sup>, Francesca Di Nunzio<sup>1</sup>  
<sup>1</sup>Institut Pasteur, Paris, France  
**Background:** HIV-1 to replicate, first has to retrotranscribe the viral RNA in DNA, which subsequently integrates into host cell chromosomes. So far, the retrotranscription (RT) activity has been considered a process that begins and ends in the cytoplasmic compartment of the host cell. Our recent study revisited the RT compartmentalization dogma highlighting that in macrophages RT occurs in the host nucleus. Nuclear RT generates functional viral DNA (vDNA), in fact, the ultimate goal of HIV-1 is integration into the host chromatin to optimize the release of high levels of viral progeny and discretely coexist with the host.  
**Methods:** To uncover the HIV-1 DNA fate in the nuclear landscape we directly tracked the vDNA and the viral RNA (vRNA) by coupling HIV-1 ANCHOR technology with RNA FISH or MCP-MS2 RNA-tagging bacterial system.  
**Results:** Our computational imaging analysis revealed that proviral forms are early located in proximity of the nuclear periphery of mitotic and non-mitotic cells. We also observed that HIV-1 infection prompts clustering formation of the host factor CPSF6, restructuring nuclear membraneless organelles, enriched in both viral proteins and speckle factors. Interestingly, we observed that integrase proteins are retained in CPSF6 clusters, while the late retrotranscribed DNA was excluded from HIV-induced membraneless organelles (HIV-1 MLOs), indicating that those structures are not proviral sites, but orchestrate viral events prior to the integration step. Of note, we show that HIV-1 MLOs are sites of nuclear RT. We also observed that HIV-1 MLOs are in the vicinity of pre-existing LEDGF clusters. Importantly, we identified that actively transcribing proviruses localize, outside HIV-1 MLOs, in LEDGF-abundant regions, known to be active chromatin sites.  
**Conclusion:** This study highlights single functional host-proviral complexes in their nuclear landscape, which is markedly restructured by HIV-1 to favor viral replication.
- 79 HIV-1 CAPSID RETAINS ITS INTEGRITY UNTIL MINUTES BEFORE UNCOATING IN THE NUCLEUS**  
**Chenglei Li**<sup>1</sup>, Ryan C. Burdick<sup>1</sup>, Kunio Nagashima<sup>2</sup>, Wei-Shau Hu<sup>3</sup>, Vinay K. Pathak<sup>1</sup>  
<sup>1</sup>National Cancer Institute, Frederick, MD, USA, <sup>2</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA, <sup>3</sup>National Institutes of Health, Frederick, MD, USA  
**Background:** HIV-1 capsid core disassembly (uncoating) is a prerequisite for viral DNA integration into the host genome and a promising target for antiviral therapy. We recently developed a method to directly label capsid protein (CA) with green fluorescent protein (GFP-CA) in infectious viral complexes and reported that HIV-1 cores that retained >94% of their CA entered the nucleus and uncoated near their integration site  $\leq 1.5$  hours before integration. However, whether the nuclear capsids lost their integrity by rupturing or a small loss of CA before capsid disassembly was unclear.  
**Methods:** We utilized a previously reported vector in which GFP is inserted in HIV-1 Gag (iGFP); proteolytic processing efficiently releases GFP, some of which remains trapped inside capsids and serves as a fluid phase content marker that is released when the capsids lose their integrity. We used live-cell imaging to track GFP and core-associated mRuby-tagged cleavage and polyadenylation specificity factor 6 (mRuby-CPSF6).  
**Results:** We found that nuclear capsids retained their integrity until shortly before integration and lost their GFP content marker  $\sim 1-3$  minutes before loss of capsid-associated mRuby-CPSF6. In contrast, when CA was tagged with GFP, loss of GFP and mRuby-CPSF6 occurred simultaneously. Thus, capsids retain their integrity until just minutes before uncoating.  
**Conclusion:** Our results indicate that HIV-1 evolved to retain its capsid integrity and maintain a separation between macromolecules in the viral core and the nuclear environment until uncoating occurs just before integration. These observations imply that intact HIV-1 capsids are imported through nuclear pores, that reverse transcription occurs in an intact capsid, and that interactions between the preintegration complex and LEDGF/p75, and possibly other host factors that facilitate integration, must occur within a short time frame between uncoating and integration.
- 80 TRAFFICKING OF HIV-1 ENVELOPE TO THE EHD1/MICAL-L1 TUBULAR-SORTING ENDOSOME**  
**Lingmei Ding**<sup>1</sup>, Grigoriy Lerner<sup>1</sup>, Boris Anokhin<sup>1</sup>, Nicholas Weaver<sup>1</sup>, Paul Spearman<sup>1</sup>  
<sup>1</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA  
**Background:** HIV-1 Env is directed to the plasma membrane (PM) through the secretory pathway, and then is rapidly endocytosed to early endosomal compartments. We have previously described the trafficking of Env to the endosomal recycling compartment (ERC). In this study, we sought to further define the components of the ERC that are required for incorporation of Env into HIV-1 particles. Sorting tubules enriched in phosphatidylinositol (4,5) bisphosphate (PIP2), Eps 15 homology domain-containing protein 1 (EHD1) and molecule interacting with CasL-like protein 1 (MICAL-L1) have been described. We sought to define the role of MICAL-L1/EHD1 tubular sorting endosomes in HIV-1 Env incorporation and replication.  
**Methods:** By employing pre-warmed paraformaldehyde and low concentrations of detergent, we were able to reproduce the work of others demonstrating long tubular EHD1- and MICAL-L1-positive compartments. We then performed colocalization analysis with markers of tubular endosomes and HIV-1 Env. We used fluorogen-activated peptide (FAP) tagging to evaluate the kinetics of movement of Env to this compartment in living cells. We then used shRNA to deplete MICAL-L1 and EHD1 in HeLa cells and the H9 T cell line, and examined the incorporation of Env into particles and replication curves in wildtype vs. knockdown cells.  
**Results:** Live cell TIRF microscopy revealed that pulse-labeled Env on the PM is rapidly segregated into PIP2-enriched tubules underlying the PM. In lightly-fixed cells, fluorescence colocalization analysis revealed a striking colocalization of HIV-1 Env with Rab10, EHD1, and MICAL-L1 in tubular sorting endosomes. Trafficking of Env lacking the cytoplasmic tail to tubular sorting endosomes, in contrast, was markedly diminished as compared with wildtype Env. Knockdown of EHD1 or MICAL-L1 in HeLa cells had little effect on Env incorporation. Strikingly, however, knockdown in H9 T cells resulted in production of particles with a deficiency of Env incorporation. Replication of HIV-1 was markedly diminished in EHD1- or MICAL-L1-depleted H9 cells as compared to control shRNA-treated cells.  
**Conclusion:** We show here for the first time that Env colocalizes strongly with Rab10/EHD1/MICAL-L1-associated sorting tubules, and that Env particle incorporation and HIV-1 replication are dependent on EHD1 and MICAL-L1. We postulate that the tubular endosome compartment plays an important role in Env endocytosis and slow recycling back to specific sites on the PM for virus assembly.
- 81 A COMPREHENSIVE CRISPR SCREEN FOR HIV DEPENDENCY FACTORS**  
**Vanessa R. Montoya**<sup>1</sup>, Abby Felton<sup>1</sup>, Molly OhAinle<sup>1</sup>, Michael Emerman<sup>1</sup>  
<sup>1</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA  
**Background:** At each stage of the HIV life cycle, host cellular proteins are hijacked by the virus to establish and enhance infection. Although there have been many host factors identified to be important for supporting HIV infection (HIV dependency factors), there is still an incomplete understanding of all host factors involved.  
**Methods:** To comprehensively identify genes that encode these dependency factors, the Emerman Lab has developed a virus-packageable HIV-CRISPR screen that utilizes a lentiviral vector containing a repaired long terminal repeat and is thus able to package into new virions. Packaging of these guideRNAs into nascent virions serves as barcodes to identify which gene targets are required for successful HIV infection. Here, we have performed two independent HIV-CRISPR screens to comprehensively study cellular factors at the genome-wide level, using the Toronto Knockout version 3 (TKOv3) library, and targeted human epigenetic/epigenetic (HuEpi) library, in Jurkat T lymphocyte cells. We then curated the results of the top  $\sim 400$  hits to make new libraries to be used to interrogate HIV dependency factors across multiple HIV strains.  
**Results:** As positive controls, many known HIV dependency factors across multiple parts of the virus cycle were identified including the HIV receptor, co-receptor, LEDGF/p75, Nfkb, and many genes encoding components of the Mediator complex. Notably, there were also numerous genes not previously reported to play a role in HIV biology involved in protein degradation, as well as epigenetic factors such MEN1, KMT2A, and KMT2D. Therefore, this screening approach is sensitive enough to identify host factors for HIV involved at all parts of the life-cycle and provides ample opportunity to investigate novel gene roles

in HIV replication. Initial validation experiments confirm the involvement of top hits of the screen in HIV replication.

**Conclusion:** This iterative screening approach has repeatedly identified specific genes that may play novel biological roles during HIV infection. Using these data to inform creation of a focused library of presumed dependency factors, I am now conducting HIV-CRISPR screens and am validating important gene candidates, to create a comprehensive list of dependency factors common across cell types for multiple strains of HIV-1. This will both advance our understanding of the HIV-1 life cycle by identifying novel dependency factors required at different stages of the life cycle and has potential to inform therapeutic and curative



**Figure 1.** ZapK0-Jurkat-CCR5 cells containing the TKOv3 or HuEpi CRISPR knockout libraries were infected with HIV-1<sub>LAI</sub> in duplicate infections. Viral RNA and genomic DNA were collected 3 days post infection and sgRNA sequences present in virions (vRNA) and genomic DNA (gDNA) were quantified through RT-PCR/PCR and deep sequencing.

## 82 EARLY bNAb THERAPY IN SHIVAD8-E0-INFECTED RHESUS MACAQUES

**Joana Dias**<sup>1</sup>, Mangaiarkaras Asokan<sup>1</sup>, David R. Ambrozak<sup>1</sup>, Lucio Gama<sup>1</sup>, Jianfei Hu<sup>1</sup>, Daniel C. Douek<sup>1</sup>, Slim Fourati<sup>2</sup>, Rafick-Pierre Sékaly<sup>2</sup>, John-Paul Todd<sup>1</sup>, Yoshiaki Nishimura<sup>1</sup>, Malcolm A. Martin<sup>1</sup>, Jeffrey D. Lifson<sup>3</sup>, Amarendra Pegu<sup>1</sup>, John R. Mascola<sup>1</sup>, Richard A. Koup<sup>1</sup>, for the Vaccine Research Center, National Institutes of Health

<sup>1</sup>National Institutes of Health, Bethesda, MD, USA, <sup>2</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>3</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA

**Background:** Co-administration of the anti-HIV-1 bNAbs 10-1074 and 3BNC117 to SHIV-infected monkeys at days 3, 10, and 17 post-challenge led to long-term CD8+ T cell-mediated control of infection in half of the monkeys (Nishimura et al., Nature, 2017). A possible mechanism behind virus control is that bNAbs form immune complexes with SHIV, leading to its cross-presentation to CD8+ T cells and more robust immune responses. Here, we studied the contribution of immune complexes to the antiviral effect of early bNAb therapy.

**Methods:** SHIVAD8-E0 intrarectally-challenged NHPs were not treated (n=6) or treated at days 3, 10, and 17 post-challenge with either WT VRC07-523-LS and PGT121 (n=6) or their DEL mutants (n=6), which show increased binding to FcγRs in vitro.

**Results:** Five each of the 6 untreated or WT bNAb-treated monkeys became infected, but WT bNAb-treated monkeys suppressed virus for the first 8-14 weeks post-challenge. Viremia occurred after plasma bNAb levels declined. However, upon rebound, the peak and set point viral loads in these monkeys were indistinguishable from the untreated monkeys up to 124 weeks post-challenge. In contrast, only 3 monkeys treated with the DEL bNAbs have rebounded so far. This occurred earlier than in the WT bNAb-treated monkeys (at 5-6 weeks post-challenge), associated with poor plasma pharmacokinetics of the DEL bNAbs. The other 3 DEL bNAb-treated monkeys have not rebounded 68 weeks post-challenge, despite absence of circulating bNAbs. Lymph node SIV-specific CD8+ T cell responses developed later in treated monkeys than in untreated animals, consistent with delayed plasma viremia upon bNAb therapy. RNA sequencing analysis of antigen-presenting cells from lymph nodes revealed that treated monkeys developed a specific transcriptomic profile at week 2 post-challenge that persisted in DEL bNAb-treated monkeys through week 8 but was absent in untreated and WT bNAb-treated monkeys at the same timepoint.

**Conclusion:** No long-term differences in viral control were observed between untreated and WT bNAb-treated monkeys but 3 DEL bNAb-treated aviremic monkeys have not rebounded and are being studied more in depth to determine if they are controlling or completely free of virus. RNA sequencing analysis will be expanded to CD8+ T cell subsets to determine the effect of bNAb treatment in cell populations downstream of antigen-presenting cells, and microscopy will

be conducted to determine the presence and location of the virus and infused bNAbs in the lymph nodes of these animals.

## 83 IMMUNE CORRELATES OF POSTTREATMENT CONTROL IN SHIV-INFECTED INFANT MACAQUES

**Veronica Obregon-Perko**<sup>1</sup>, Bhrugu Yagnik<sup>2</sup>, Tiffany M. Styles<sup>2</sup>, Katherine M. Bricker<sup>1</sup>, Gloria Mensah<sup>1</sup>, Stella J. Berendam<sup>3</sup>, Katharine J. Bar<sup>4</sup>, George Shaw<sup>4</sup>, Guido Silvestri<sup>2</sup>, Genevieve Fouda<sup>3</sup>, Sallie R. Permar<sup>3</sup>, Rama R. Amara<sup>2</sup>, Ann Chahroudi<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Yerkes National Primate Research Center, Atlanta, GA, USA, <sup>3</sup>Duke Human Vaccine Institute, Durham, NC, USA, <sup>4</sup>University of Pennsylvania, Philadelphia, PA, USA

**Background:** Breastfeeding transmission accounts for the majority of new pediatric HIV infections and commits infants to lifelong ART, as interruption is typically followed by return of replication and repopulation of reservoirs. Previous studies in adult humans and animal models have identified correlates of viral control following analytical treatment interruption (ATI). However, it is critical to understand the kinetics and predictors of viral rebound in the setting of breastfeeding transmission to inform the development of novel pediatric-focused remission strategies.

**Methods:** At 4 wks of age, Mamu-B\*08-/B\*17-/A\*01- or + rhesus macaques were orally administered SHIV.C.CH505.375H.dCT and placed on daily ART at 2 wpi (intermediate, n=10) or 8 wpi (Late, n=10). ART was interrupted after 1 yr to assess viral rebound. Blood and lymph nodes (LN) were collected throughout the study for flow cytometry and viral measurements. Spearman correlations were used to identify associations between viral control and over 30 immune parameters measured pre-ATI.

**Results:** Pre-ATI cell-associated SHIV DNA levels were 14-fold lower in blood (p=0.0003) and 60-fold lower in LN (p=0.0001) in animals that initiated ART earlier in infection, but this did not significantly delay time to viral rebound when compared to animals treated later. In both groups, rebound viremia was detected within 7-35 d post-ATI in all but 1 non-rebounder macaque. Post-treatment control (PTC) of viremia within 98 d of ATI was observed in 9/9 Mamu-A\*01+ macaques, an allele known to be associated with CTL responses to an immunodominant Gag epitope. However, PTC was also seen in 5/11 Mamu-A\*01- macaques, suggesting viral control could be mediated by other mechanisms. We found that the frequency of Granzyme B+ Ki67+ NK cells (CD3- NKG2A+) in the blood pre-ATI was negatively correlated with area under the curve (AUC) for viral loads during rebound in Mamu-A\*01- macaques (r=-0.8424, raw p=0.004). In addition, Mamu-A\*01- animals with lower rebound viral load AUC tended to have a higher percentage of anti-Gag IFN-γ-producing CD4+ T cells in the blood (r=-0.6126, raw p=0.05) and LN (r=-0.8424, raw p=0.01) prior to ATI.

**Conclusion:** This work provides novel insight into the predictors of PTC in a preclinical NHP model of pediatric HIV-1 infection. Our findings highlight aspects of innate and adaptive immunity may be critical in controlling viral rebound and should be studied further in the development of remission strategies in HIV-1-infected children.

## 84 SIVΔGY INFECTION INDUCES ELITE CONTROL AND RESISTANCE TO SHIV HETEROLOGOUS CHALLENGE

**Khader Ghneim**<sup>1</sup>, Nicholas Maness<sup>2</sup>, Pyone Aye<sup>2</sup>, Workineh Torben<sup>2</sup>, Faith Schiro<sup>2</sup>, Brandon Keele<sup>3</sup>, Mark Marsh<sup>4</sup>, G. Lynn Law<sup>5</sup>, Michael Gale<sup>5</sup>, Rafick-Pierre Sékaly<sup>1</sup>, James Hoxie<sup>6</sup>, Susan Pereira Ribeiro<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Tulane National Primate Research Center, Covington, LA, USA, <sup>3</sup>NCI -3AIDS & Cancer Virus Program, Frederick MD, USA, <sup>4</sup>UCL Great Ormond Street Institute of Child Health, London, UK, <sup>5</sup>University of Washington, Seattle, WA, USA, <sup>6</sup>University of Pennsylvania, Philadelphia, PA, USA

**Background:** HIV reservoir persistence is an obstacle to cure. Elite controllers (ECs) suppress virus in the absence of anti-retroviral drugs. Immunologic mechanisms that lead to viral control and interventions that could reduce or eliminate HIV reservoirs in ECs are unknown. Relevant models of EC in nonhuman primates (NHP) could be critical to address these questions. Our lab has described and published a unique NHP model of elite SIV control termed ΔGY. This variant of SIVmac239 contains a 2 amino acid deletion in a Tyr-dependent Env trafficking motif and is replication fit but susceptible to host control through cellular immune responses (CTL and/or ADCC) in the absence of neutralizing antibodies.

**Methods:** Pigtail macaques were infected with  $\Delta$ GY (n=8) or SIVmac239 (n=4) and PBMC, lymph node (LN), duodenal tissues and plasma were collected longitudinally to identify transcriptional signatures and cytokines correlating with viral control, respectively (Fig1). Animals were challenged at week 80 with SHIV-SF162P3N.

**Results:** Gene signatures (all tissues) and cytokine/chemokines profiles at day 2 post-infection discriminated both groups while peak viral loads were similar. Compared to SIVmac239,  $\Delta$ GY-infected animals presented decreased inflammasome signature/cytokines (IL1b, IL18), decreased anti-inflammatory signature/cytokines (TGFb1, TGFb2) and increased homeostatic signaling downstream of IL2. Additionally, NLRX1, an early antagonist of type I IFN anti-viral signaling, was decreased in  $\Delta$ GY-animals and this was concomitant with higher CD8 effector function signatures (TBX21, IFNG, GZMB), lower T cell exhaustion (TOX, PDCD1) and preserved chemokine signaling (CXCL1, CXCL10-12). Correlates of these findings in  $\Delta$ GY-infected animals included 1) control of viremia by 10-20 weeks; 2) normal numbers of CD4 T cells in blood and gut; and 3) lack of immune activation signatures. Additionally, when 6  $\Delta$ GY-controllers were challenged i.v. at 80 weeks with SHIV-SF162P3N, they controlled the challenge for more than 2 years (set points of  $\leq 10^2$ -3 RNA cps/mL) in contrast to 4 naive controls (set points  $10^5$ - $10^6$  cps/mL).

**Conclusion:**  $\Delta$ GY infection leads to a preserved adaptive immune response signature, in association with sustained viral control, CD4 T cell counts and resistance to a pathogenic i.v. heterologous challenge. Understanding of the mechanisms by which  $\Delta$ GY infection can augment host immune responses to resist challenge viruses could have important implications for both HIV vaccine and pathogenesis fields.

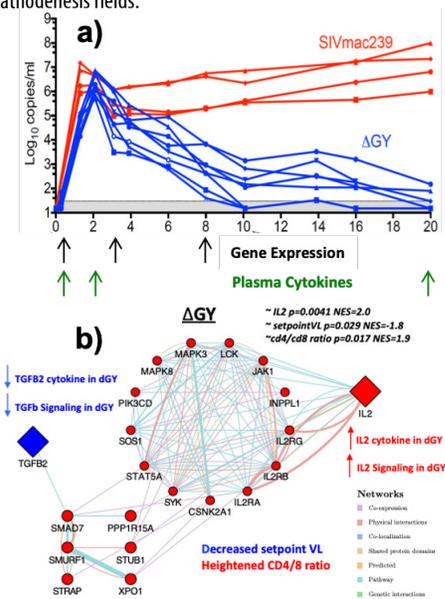


Fig1. a)  $\Delta$ GY infected animals control viral replication mimicking human Elite controllers; b) Gene signatures associated to heightened IL2 signature and decreased TGFb signaling is the hallmark of  $\Delta$ GY infection as compared to SIVmac239 infected animals.

targeting the V3 base on a closed Env. In the CD4-bound conformation, the V3 becomes fully accessible and conformationally dynamic. Functional relevance of these intermediate V3 conformations and their potential for broad neutralization still remain to be resolved.

**Methods:** Here we applied the Designed Ankyrin Repeat Protein (DARPin) technology to select DARPins targeting HIV-1 Env by Ribosome Display. Hits were screened for V3 binders with broad neutralizing capacity. Neutralization breadth was assessed on a 42-multiclade Tier-2 virus panel in the TZM-bl assay. DARPin epitopes were characterized by binding to Env derivatives, deep mutational Env scanning, X-ray crystallography, cryo-EM and molecular dynamics.

**Results:** We identified 8 distinct V3 specific DARPins with exceptional neutralization breadth of up to 93%. Unlike V3-glycan bnAbs, these broadly neutralizing DARPins (bnDs) bound V3 solely on open but not closed Env. X-ray and cryo-EM structure analyses of bnD.8 and bnD.9 revealed binding to a 3-turn amphipathic alpha-helix in the C-strand of V3 spanning residues 314 to 324. We termed this novel conformation  $\alpha$ V3C. Remarkably, the  $\alpha$ V3C helix was trapped by two unrelated bnDs and observed both in complex with V3 peptide and open, CD4-triggered Env trimer. Molecular dynamics simulations indicated that the  $\alpha$ V3C helix remains stable in the absence of the bnDs, emphasizing a functional relevance. Comprehensive Env mutation scanning underlined functional importance. Escape mutations accumulated on the contact face of the helix, but no enrichment of putative helix disturbing mutations occurred.

**Conclusion:** The discovery of post-CD4 engagement acting V3 inhibitors with extraordinary breadth is remarkable. The helical V3 conformation they define sheds light on V3 conformational dynamics after CD4 engagement and reveals a new site of vulnerability on HIV-1 Env. Our findings emphasize the importance of V3 and the open Env conformation as a target for inhibitors and mark the newly defined  $\alpha$ V3C helix as a blueprint for epitope-based vaccine design.

86



## AN Env-gag mRNA VACCINE PROTECTS MACAQUES FROM HETEROLOGOUS TIER-2 SHIV INFECTION

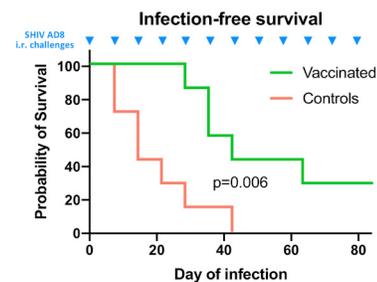
Peng Zhang<sup>1</sup>, Elisabeth Narayanan<sup>2</sup>, Shilei Ding<sup>3</sup>, Madhu Prabhakaran<sup>1</sup>, Yaroslav Tsybovsky<sup>4</sup>, Richard A. Koup<sup>1</sup>, Malcolm A. Martin<sup>5</sup>, Johnathan Misamore<sup>6</sup>, Adrian McDermott<sup>5</sup>, John R. Mascola<sup>1</sup>, Andrea Carfi<sup>7</sup>, Andrés Finzi<sup>3</sup>, Anthony S. Fauci<sup>1</sup>, Paolo Lusso<sup>1</sup>, for the National Institute of Allergy and Infectious Diseases <sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>2</sup>Maasstad Hospital, Rotterdam, Netherlands, <sup>3</sup>Université de Montréal, Montreal, Canada, <sup>4</sup>National Cancer Institute, Bethesda, MD, USA, <sup>5</sup>National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, <sup>6</sup>BIOQUAL, Inc, Rockville, MD, USA, <sup>7</sup>Aalborg University Hospital, Aalborg, Denmark

**Background:** The development of a preventive vaccine remains a critical priority for ending the HIV/AIDS pandemic. Critical improvements in mRNA technology, as attested by recent successes in preventing COVID-19 disease, led us to develop an mRNA platform for HIV vaccines.

**Methods:** In this regard, we designed an mRNA vaccine with different HIV-1 envelope mRNAs from 3 different clades co-formulated with SIV gag mRNA, which can assemble virus like particles (VLPs) in vivo. Rhesus macaques were primed with a transmitted-founder clade-B Env lacking the 276 N-glycan followed by multiple glycan-repaired autologous and bivalent heterologous (clades A and C) booster immunizations.

**Results:** Immunized animals rapidly developed autologous neutralizing antibodies and eventually, after the second heterologous boost, cross-reactive tier-2 neutralizing antibodies, albeit at low titers. Vaccinated animals were protected from repeated low-dose rectal challenges with a heterologous tier-2 simian-human immunodeficiency virus (AD8). Protection was correlated with the presence of antibodies to the CD4-binding site.

**Conclusion:** Thus, the Gag-Env VLP mRNA platform offers a promising strategy for the development of an HIV-1 vaccine.



85



## TRAPPING THE HIV-1 V3 LOOP IN A HELICAL CONFORMATION ENABLES BROAD NEUTRALIZATION

Matthias Glögl<sup>1</sup>, Nikolas Friedrich<sup>1</sup>, Young Do Kwon<sup>2</sup>, Thomas Lemmin<sup>1</sup>, Gabriele Cerutti<sup>3</sup>, Jason Gorman<sup>2</sup>, Liridona Maliqi<sup>1</sup>, Peer Mittl<sup>1</sup>, Caio Foulkes<sup>1</sup>, Thomas Reinberg<sup>1</sup>, Birgit Dreier<sup>1</sup>, Lawrence Shapiro<sup>2</sup>, Peter D. Kwong<sup>2</sup>, Andreas Plückthun<sup>1</sup>, Alexandra Trkola<sup>1</sup>

<sup>1</sup>University of Zurich, Zurich, Switzerland, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>3</sup>Columbia University, New York, NY, USA

**Background:** HIV-1 entry depends on the interaction of the envelope (Env) protein's variable loop 3 (V3) with a co-receptor. While this indispensable function renders the V3 a key target for inhibition, the vigorous antibody response elicited in natural infection is largely non-neutralizing owing to conformational masking of the V3 crown on the prefusion-closed Env trimer. Only a fraction of individuals develops broadly neutralizing antibodies (bnAbs)

**87 ISLATRAVIR PK THRESHOLD & DOSE SELECTION FOR MONTHLY ORAL HIV-1 PrEP**

**Munjal Patel<sup>1</sup>**, Xiaowei Zang<sup>1</sup>, Youfang Cao<sup>1</sup>, Randolph P. Matthews<sup>1</sup>, Rebeca M. Plank<sup>1</sup>, Peter Sklar<sup>1</sup>, Jay A. Grobler<sup>1</sup>, Michael N. Robertson<sup>1</sup>, Ryan Vargo<sup>1</sup>  
<sup>1</sup>Merck & Co, Inc, Kenilworth, NJ, USA

**Background:** Innovations in HIV-1 pre-exposure prophylaxis (PrEP) are needed to address the global HIV epidemic and meet the diverse needs of individuals at risk of acquiring HIV-1. Islatravir (ISL) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1. In this PK/PD work, we present the data that defined the exposure threshold for ISL for PrEP and the corresponding oral once monthly (QM) dose for the phase 3 clinical development program.

**Methods:** The lower efficacious exposure threshold for ISL PrEP efficacy was based on (1) the estimated protective ISL-triphosphate (ISL-TP) EC<sub>50</sub> from a study of male rhesus macaque undergoing SHIV intra-rectal challenge using once weekly oral ISL, (2) the minimum efficacious ISL-TP concentration in a Phase 1b proof-of-concept trial (NCT02217904) in treatment-naïve adults with HIV-1, and (3) relevant data from the literature regarding the protective concentrations of FTC/TDF. Population PK simulations were conducted using data from the Phase 1 and 2 studies of ISL to determine the phase 3 oral QM dose.

**Results:** Totality of the data from the rhesus macaque study, the Phase 1b trial, and benchmarking PK exposures from TDF-DP resulting from both pre-clinical and clinical studies suggest that full efficacy for HIV-1 prevention is achieved with approximate inhibitory quotient (IQ) of ~1-5 (Table). Based on these observations, the efficacious exposure threshold for ISL PrEP was set at 0.05 pmol/10<sup>6</sup> cells in PBMCs, which is ~5-fold above the in vitro IC<sub>50</sub> (0.00974 pmol/10<sup>6</sup> cells) of ISL-TP against wild type HIV-1. In an ongoing Phase 2 trial (NCT04003103), the observed mean ISL-TP exposure 4 weeks after a 60-mg dose was ~26 fold above the PK threshold. Additionally, population PK simulations suggest that oral ISL 60-mg QM will achieve ISL-TP concentrations well above the PK threshold for all participants following the first monthly dose. All participants at this dose are predicted to be above the PK threshold with the lower 2.5th prediction interval having an ~IQ of 17.

**Conclusion:** To provide efficacious exposures for protection against HIV-1, a 60-mg oral QM dose of ISL was selected for the Phase 3 clinical program. This dose is expected to maintain ISL-TP concentrations above the conservative PK threshold of 0.05 pmol/10<sup>6</sup> cells for all participants with sustained exposures in the event of a delayed or missed monthly dose.

| Drug               | Study Description   | Observed or Estimated Exposures   | Exposure Value (pmol/10 <sup>6</sup> PBMCs) | Inhibitory Quotient * |
|--------------------|---|---|---|-----------------------|
| ISL                | Male rhesus macaque SHIV intra-rectal challenge study using once weekly oral ISL <sup>b</sup> | Estimated ISL-TP EC <sub>50</sub> , which resulted in 92% protection from infection                             | 0.0240                                      | 2                     |
|                    | Phase 1b proof of concept trial (NCT02217904) in ART naïve participants <sup>c</sup>          | Lowest observed individual concentration associated with antiviral efficacy                                     | 0.0513                                      | 5                     |
|                    | Ongoing Phase 2 clinical trial in low-risk healthy participants (NCT04003103)                 | Observed interim mean monthly ISL-TP trough from 60 mg QM ISL   | 1.3260                                      | 136                   |
|                    | Population PK simulations of 60 mg QM ISL   | Steady state lower 2.5 <sup>th</sup> percentile of 95% prediction interval for monthly ISL-TP trough            | 0.1709                                      | 17                    |
| FTC/TDF or FTC/TAF | Male rhesus macaque SHIV intra-rectal challenge study using oral daily FTC/TDF <sup>d</sup>   | Estimated TDF-DP EC <sub>50</sub> , which resulted in 90% protection from infection                             | 0.0226                                      | ≤ 1                   |
|                    | Female rhesus macaque SHIV intravaginal challenge study using FTC/TAF <sup>e</sup>            | Observed minimum protective TDF-DP concentration  | 0.1230                                      | 3                     |
|                    | iPrEx trial conducted in men having sex with men <sup>f,g</sup>                               | Estimated TDF-DP EC <sub>50</sub> for viable cells<br>Estimated TDF-DP EC <sub>50</sub> for freshly lysed cells | 0.0160<br>0.0400                            | ≤ 1<br>≤ 1            |

\*Inhibitory quotient was derived using ratio of active intracellular concentration and respective intracellular IC<sub>50</sub>; in vitro wild type IC<sub>50</sub>: 0.00974 pmol/10<sup>6</sup> cells for ISL-TP; 0.0415 pmol/10<sup>6</sup> cells for FTC/TDF; and 0.113 pmol/10<sup>6</sup> cells for FTC/TAF; Grobler et al. *Top Antiviral Med.* 2019 May;27(1):178.  
<sup>b</sup>Markowitz et al. *JID* 2020;221:1398-406; <sup>c</sup>Scharnau D et al. *Lancet HIV* 2020;7:e164-72; <sup>d</sup>Anderson et al. *J Antimicrob Chemother* 2014;69:2470-76; <sup>e</sup>Masad J et al. *CROI 2018*, Abstract 85; <sup>f</sup>Anderson et al. *Sci. Transl. Med.* 2012;4:151ra125.

**88 NEXT-GENERATION ISLATRAVIR IMPLANTS PROJECTED TO PROVIDE YEARLY HIV PROPHYLAXIS**

**Randolph P. Matthews<sup>1</sup>**, Xiaowei Zang<sup>1</sup>, Stephanie Barrett<sup>1</sup>, Adrian Goodey<sup>1</sup>, Tycho Heimbach<sup>1</sup>, Vanessa L. Weissler<sup>1</sup>, Carlien Leysens<sup>1</sup>, Tom Reynders<sup>1</sup>, Ryan Vargo<sup>1</sup>, Yang Liu<sup>1</sup>, Robert Schwab<sup>2</sup>, Sylvie Rottey<sup>3</sup>, Michael N. Robertson<sup>1</sup>, Selwyn A. Stoch<sup>1</sup>, Marian Iwamoto<sup>1</sup>

<sup>1</sup>Merck & Co, Inc, Kenilworth, NJ, USA, <sup>2</sup>Celerion, Lincoln, NE, USA, <sup>3</sup>Ghent University Hospital, Ghent, Belgium

**Background:** Preexposure prophylaxis (PrEP) with antiretroviral drugs has demonstrated efficacy in reducing new HIV infections, although efficacy is tightly linked to good adherence, especially in women. Islatravir (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor with high potency and long t<sub>1/2z</sub>, currently in development for PrEP as an oral monthly pill. In addition, prototype islatravir implants (containing only polymer and islatravir) have demonstrated the potential for yearly administration for PrEP.

**Methods:** Radiopaque next-generation islatravir-eluting implants were studied preclinically to establish general tolerability and assess pharmacokinetics (PK) of islatravir parent and active islatravir-TP (triphosphate). These data, along with data from an SIV challenge study and from previous Phase 1 trials, formed the basis for establishing a threshold islatravir-TP concentration of 0.05 pmol/million cells in PBMCs. In this double-blind placebo-controlled multicenter Phase 1 trial, a single islatravir-eluting (48 mg, 52 mg or 56 mg) or placebo implant was placed in participants at low risk of HIV infection for 12 weeks. Safety and tolerability, as well as PK for islatravir parent and islatravir-TP from plasma and PBMCs, was collected throughout placement and for 8 weeks post removal.

**Results:** Implants were generally well tolerated, and there was no clear dose-dependent difference in implant-related adverse events (Table 1A). Active islatravir-TP levels were above target for all implants throughout implant placement (Table 1B). Data from this trial and from in vitro assessments of the ISL implants suggest that implants of >52 mg will achieve mean ISL-TP concentrations above the PK threshold at 52 weeks.

**Conclusion:** Next-generation radiopaque islatravir-eluting implants provide drug release projected to be sufficient for HIV prophylaxis for at least one year. Islatravir-eluting implants appear to be well tolerated, and the results from this trial support further study of these implants in a larger, longer Phase 2 trial. A PrEP implant could provide an attractive option for individuals in whom adherence to a daily PrEP regimen is challenging.

TABLE 1: A) Number of individuals reporting implant-related adverse events (% of total). Note this is blinded data. N=12 total per dose level; 8 on active and 4 on placebo. B) Mean islatravir-TP levels at 12 weeks.

| A   | 48 mg        | 52 mg        | 56 mg        |
|---|--------------|--------------|--------------|
| TOTAL   | 8 (67)       | 6 (50)       | 8 (67)       |
| Hematoma  | 6 (50)       | 6 (50)       | 5 (42)       |
| Erythema  | 5 (42)       | 3 (25)       | 5 (42)       |
| Tenderness  | 3 (25)       | 6 (50)       | 5 (42)       |
| Pruritis  | 6 (50)       | 3 (25)       | 7 (58)       |
| Induration  | 4 (33)       | 5 (42)       | 5 (42)       |
| B   |              |              |              |
| N   | 8            | 8            | 8            |
| Geometric Mean C85d (%GCV) (pmol/10 <sup>6</sup> cells) | 0.118 (18.3) | 0.198 (70.0) | 0.620 (49.9) |

**89 CLINICAL EVALUATION OF DRUG INTERACTIONS WITH ORAL LENACAPAVIR AND PROBE DRUGS**

**Rebecca Begley<sup>1</sup>**, Justin Lutz<sup>1</sup>, Hadas Dvory-Sobol<sup>1</sup>, Steve West<sup>1</sup>, Kristin Kawata<sup>1</sup>, John Ling<sup>1</sup>, Martin Rhee<sup>1</sup>, Polina German<sup>1</sup>  
<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA

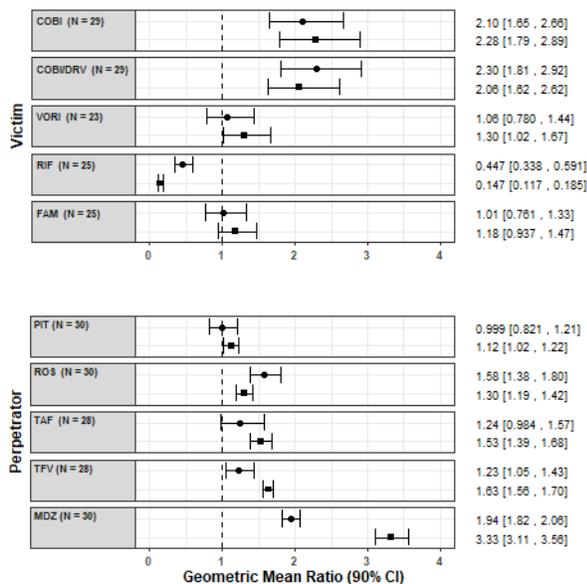
**Background:** Lenacapavir (LEN; GS-6207) is a potent, selective, first-in-class, multi-stage inhibitor of HIV-1 capsid function in clinical development as a long-acting agent for treatment and prevention of HIV-1 infection. Based on in vitro data, LEN is a substrate for P-gp, CYP3A, and UGT1A1, may inhibit P-gp, BCRP, OATP, and CYP3A, and may induce CYP3A. Also, LEN exhibits pH-dependent solubility (higher solubility at pH ≥ 6). In this Phase 1 study, we evaluated LEN drug interactions using cobicistat (COBI) +/- darunavir (DRV) as inhibitors of CYP3A/P-gp, voriconazole (VORI) as an inhibitor of CYP3A, rifampin (RIF) as an inducer of CYP/P-gp/UGT, and famotidine (FAM) as a gastric acid-reducing agent. The perpetrator interaction potential was evaluated using pitavastatin (PIT; OATP substrate), rosuvastatin (ROS; BCRP/OATP substrate), tenofovir alafenamide (TAF; P-gp substrate), and midazolam (MDZ; CYP3A substrate).

**Methods:** In separate cohorts of healthy participants (parallel study design), single oral doses of LEN (300mg) were given with and without COBI (150mg QD, Days 1-35), DRV/COBI (800mg/150mg QD, Days 1-35), VORI (400mg BID x 1 day, then 200mg BID Days 2-25), RIF (600mg QD, Days 1-25), and FAM (40mg single dose 2 h prior to LEN). In another cohort, single doses of PIT (2mg), ROS (5 mg), TAF (25mg), and MDZ (2.5mg) were given prior to and simultaneous with LEN 600mg BID x2 days, then Q3 days to rapidly achieve clinically relevant LEN exposure.

**Results:** Geometric-least squares means ratio (GLSM) and 90% confidence intervals (90% CI) for AUC<sub>∞</sub> (•) and C<sub>max</sub> (●) for combination vs substrate alone were estimated by linear mixed effect modeling: Of 223 total participants, none had serious or Grade 4 adverse events (AEs). One participant had a Grade 3 AE of elevated transaminase while receiving LEN + ROS, which led to study drug discontinuation. Most AEs were mild in severity.

**Conclusion:** Consistent with in vitro data, these results confirm that LEN is a substrate of both CYP3A and P-gp. The magnitude of inhibition via COBI, DRV/COBI, and VORI is not considered to be clinically relevant, supporting

coadministration of LEN with potent inhibitors of CYP3A and P-gp without dose modification. However, potent inducers of CYP/P-gp/UGT, such as RIF, should be avoided. LEN is not affected by gastric acid reducers. As a perpetrator, LEN would be considered a moderate inhibitor of CYP3A, and a weak inhibitor of P-gp, BCRP, with no effect on OATP. Overall, LEN has a limited drug interaction potential.



## 90 PK AND SAFETY OF HIGH-DOSE RIFAMPICIN IN TB/HIV COINFECTED PATIENTS ON EFV OR DTG

Christine Sekaggya-Wiltshire<sup>1</sup>, Ruth Nabiser<sup>1</sup>, Joseph Musaazi<sup>1</sup>, Florence Aber<sup>1</sup>, Brian Otaalo<sup>1</sup>, Mohammed Lamorde<sup>1</sup>, Paolo Denti<sup>2</sup>, Rob Aarnoutse<sup>3</sup>, Kelly Dooley<sup>4</sup>, Derek J. Sloan<sup>5</sup>

<sup>1</sup>Infectious Diseases Institute, Kampala, Uganda, <sup>2</sup>University of Cape Town, Cape Town, South Africa, <sup>3</sup>Radboud University, Nijmegen, Netherlands, <sup>4</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>5</sup>University of St Andrews, St Andrews, UK

**Background:** Recent data suggest higher doses of rifamycins may increase efficacy of TB regimens and reduce the required duration for treatment. Dose escalation of rifampicin, the most widely-used rifamycin, have mainly been studied in HIV-negative TB patients. TB-HIV co-treatment increases risk for drug-drug interactions and drug-related toxicities. In TB-HIV co-infected patients, we studied the safety of a higher dose rifampicin and its effect on the pharmacokinetics (PK) of efavirenz (EFV) or dolutegravir (DTG).

**Methods:** A randomized open-label Phase IIb clinical trial among TB-HIV co-infected adults attending an HIV clinic in Uganda. Newly-diagnosed TB patients were randomized to either standard (10 mg/kg) or higher (35 mg/kg) dose rifampicin alongside standard TB treatment. ART-naïve patients were randomly assigned to DTG- or EFV-based ART regimens. Patients on ART (DTG or EFV) at enrollment continued on the same ART regimen however DTG was adjusted from once-daily to twice-daily dosing. PK sampling was performed at week 6 of TB treatment with sampling for DTG 12 hours after the last dose ( $C_{trough}$ ) and a mid-dose concentration was obtained for EFV. P-values and 95% CI were obtained using unadjusted linear regression on log-transformed PK values with treatment arm as the only covariate.

**Results:** Of 120 patients enrolled median age was 36 (30-43) years and 74 (61.7%) were men. Geometric mean (95% CI)  $C_{12}$  for DTG were similar in high- and standard-dose rifampicin arms (0.32 [0.11-0.95] mg/L and 0.30 [0.11-0.82] mg/L respectively),  $P=0.91$ ). There was a non-significant trend towards lower efavirenz mid-dose concentrations in the high-dose rifampicin arm, but variability was high, [3.68 [2.17-6.25] mg/L and 7.27 [4.65-11.37] mg/L respectively,  $P=0.054$ ]. (Table 1). Grade 3-4 adverse events were similar in the high- vs. standard-dose rifampicin arms (6/71 vs. 5/84). Of these, 6 were serious adverse events (SAE); 3 on high-dose rifampicin+DTG and 3 on standard-dose rifampicin+DTG. There were no SAEs in the efavirenz arms. Sputum conversion at week 8 was higher in high-dose versus standard-dose arms (25/29 [86.2%] vs. 22/35 [62.9%]).

**Conclusion:** Compared to the standard dose, a three-fold dose increase for rifampicin did not increase risk of adverse events in patients receiving ART, appeared to improve culture conversion, and did not alter the magnitude of the drug-drug interaction with DTG. High-dose rifampicin interactions with EFV require further exploration.

Table 1: Dolutegravir (DTG) trough and Efavirenz (EFV) mid-dose concentration in patients on high dose vs standard dose rifampicin.

|                          | DTG group                             |   | EFV group                             |  |
|--------------------------|---------------------------------------|---|---------------------------------------|--|
|                          | Arm 1A<br>High dose<br>(RIF 35 mg/kg) | Arm 1B<br>Standard dose<br>(RIF 10 mg/kg) | Arm 2A<br>High dose<br>(RIF 35 mg/kg) | Arm 2B<br>Regular dose<br>(RIF 10 mg/kg) |
| Number randomized, n     | 30                                    | 34  | 25                                    | 29                                       |
| <b>PK concentrations</b> |                                       |   |                                       |  |
| Geometric Mean           | 0.32                                  | 0.30                                      | 0.33                                  | 0.60                                     |
| 95% Confidence Interval* | 0.11 – 0.95                           | 0.11 – 0.82                               | 0.02 – 4.87                           | 0.06 – 6.02                              |
| P-value                  | 0.918                                 |   | 0.72                                  |  |

RIF – Rifampicin, DTG – Dolutegravir, CI = Confidence Interval  
DTG concentrations represented as trough drug concentration ( $C_{trough}$ ) and EFV as mid-dose

## 91 PK OF DOSE-ADJUSTED EMERGENCY CONTRACEPTION WITH EFV-BASED ART IN ACTG 5375

Kimberly K. Scarsi<sup>1</sup>, Laura M. Smeaton<sup>2</sup>, Anthony T. Podany<sup>1</sup>, Maxine Olefsky<sup>2</sup>, Elizabeth Woolley<sup>3</sup>, Elizabeth Barr<sup>4</sup>, Kayla Campbell<sup>1</sup>, Sivaporn Gatechomp<sup>5</sup>, Jeffrey Jeppson<sup>1</sup>, Sajeeda Mawlana<sup>6</sup>, Khuanchai Supparatpinyo<sup>7</sup>, Catherine Godfrey<sup>8</sup>, Susan E. Cohn<sup>9</sup>, Rosie Mngqibisa<sup>6</sup>, for the AIDS Clinical Trials Group A5375 Study Team

<sup>1</sup>University of Nebraska Medical Center, Omaha, NE, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>DLH Corporation, Silver Spring, MD, USA, <sup>4</sup>Office of Research on Women's Health, Bethesda, MD, USA, <sup>5</sup>Thai Red Cross AIDS Research Center, Bangkok, Thailand, <sup>6</sup>Enhancing Care Foundation, Durban, South Africa, <sup>7</sup>Chiang Mai University, Chiang Mai, Thailand, <sup>8</sup>Office of the Global AIDS Coordinator, Washington, DC, USA, <sup>9</sup>Northwestern University, Chicago, IL, USA

**Background:** Levonorgestrel (LNG) emergency contraception (EC), when administered as a single dose, prevents pregnancy by delaying ovulation after unprotected sex that could lead to pregnancy. LNG area under the concentration time curve (AUC) is reduced 57% when coadministered with EFV in healthy volunteers. Some guidelines recommend dose-adjustment of LNG EC from 1.5mg to 3mg when combined with EFV, but this strategy has not been assessed in pharmacokinetic (PK) or clinical studies. We hypothesized that doubling the dose of LNG EC to 3mg would increase LNG exposure in individuals receiving EFV-based ART.

**Methods:** ACTG study A5375 was a multicenter, parallel group, PK evaluation of pre-menopausal females,  $\geq 16$  years old, without an indication for EC at entry. Participants with HIV and receiving EFV plus two NRTIs were randomized (1:2 ratio) to either LNG 1.5mg (n=17) or 3mg (n=35), given as a single dose with food. Plasma was collected pre-dose, then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48h post-LNG dose. Participants were followed for 4 weeks to assess adverse events. LNG concentrations were measured by LC-MS/MS and PK parameters calculated by non-compartmental methods. PK parameters were compared between dosing groups by geometric mean ratio (GMR; 90% CI).

**Results:** Participants (n=52) enrolled between Sept and Dec 2019. All self-identified as cis-women, 29 (56%) Asian, 19 (37%) African, and 4 (8%) Latina, with mean (SD) BMI 23.9 (5.6) kg/m<sup>2</sup>. The Table summarizes LNG PK parameters. The maximum concentration ( $C_{max}$ ) was 51% higher after LNG 3mg (24.9 ng/mL) compared to 1.5mg (15.1 ng/mL), and the 48h concentration was 133% higher (0.6 vs 0.3 ng/mL, respectively). The AUC over 8 hours was 66% higher in the 3mg group and remained 74-77% higher over 24 and 48 hours post-dose. Other PK parameters did not differ between groups (Table). No targeted or severe adverse events were reported.

**Conclusion:** EFV induced LNG metabolism, as demonstrated by a 12h half-life in both study groups, compared to 27h in historic data in the absence of a drug-drug interaction (Praditpan et al, Contraception 2017). Dose adjustment of LNG EC from 1.5mg to 3mg successfully increased LNG exposure in women receiving EFV-based ART. In combination with EFV-based ART, LNG 3mg resulted in a higher  $C_{max}$ , both herein and compared to historic data of LNG 1.5mg (18.2 ng/mL; Praditpan et al). As  $C_{max}$  is the proposed PK parameter associated with EC effectiveness, our data support the dose-adjustment of LNG EC to 3mg in women receiving EFV-based

Levonorgestrel pharmacokinetic parameters when coadministered with efavirenz-based ART

|                                   | LNG 1.5mg<br>(n=17)<br>Median (Q1, Q3) | LNG 3mg<br>(n=35)<br>Median (Q1, Q3) | GMR (90% CI)<br>LNG 3mg:LNG 1.5mg | p-value* |
|-----------------------------------|--|--------------------------------------|-----------------------------------|----------|
| C <sub>max</sub> (ng/mL)          | 15.1<br>(11.2, 24.0)                   | 24.9<br>(16.2, 29.6)                 | 1.51<br>(1.17, 1.95)              | 0.016    |
| T <sub>max</sub> (h)              | 1.5<br>(1.5, 2.1)                      | 2<br>(1.5, 3.0)                      | NA                                | 0.378    |
| C <sub>50h</sub> (ng/mL)          | 0.3<br>(0.2, 0.4)                      | 0.6<br>(0.3, 1.1)                    | 2.33<br>(1.49, 3.64)              | 0.006    |
| Vd/F (L)                          | 276.7<br>(118.3, 411.8)                | 294.9<br>(208.7, 489.5)              | 1.20<br>(0.87, 1.66)              | 0.416    |
| T <sub>1/2</sub> (h)              | 12.1<br>(8.6, 13.7)                    | 11.8<br>(10.6, 13.8)                 | NA                                | 0.523    |
| CL/F (L/h)                        | 12.6<br>(10.4, 21.1)                   | 15.2<br>(12.6, 27.7)                 | 1.11<br>(0.82, 1.52)              | 0.363    |
| AUC <sub>0-8h</sub><br>(h*ng/mL)  | 52.1<br>(36.7, 88.3)                   | 102.1<br>(64.5, 114.7)               | 1.66<br>(1.27, 2.18)              | 0.013    |
| AUC <sub>0-24h</sub><br>(h*ng/mL) | 81.6<br>(56.1, 128.5)                  | 153.4<br>(100.1, 190.5)              | 1.74<br>(1.29, 2.33)              | 0.011    |
| AUC <sub>0-48h</sub><br>(h*ng/mL) | 99.0<br>(66.4, 141.3)                  | 180.3<br>(106.9, 216.8)              | 1.77<br>(1.31, 2.40)              | 0.009    |

\* Exact Wilcoxon Rank Sum  
Abbreviations not defined in abstract: C<sub>50h</sub>, concentration 48 hours post-dose; CL/F, apparent oral clearance; NA, not applicable; Q1, 25<sup>th</sup> percentile; Q3, 75<sup>th</sup> percentile; T<sub>1/2</sub>, elimination half-life; T<sub>max</sub>, time of maximum concentration; Vd/F, apparent volume of distribution.

Table. Odds ratio (OR) and adjusted OR (aOR) of risk of future HIV viral load >20 copies/mL by concentration of emtricitabine triphosphate in dried blood spots at current visit in the study population (N=667), and after further adjusting for 3-day self-reported adherence (100% vs. <100%).

| FTC-TP (fmol/punch)                                    | Paired assessments n (%) | OR (95% CI)     | p-value | *aOR (95% CI)   | p-value |
|--|--------------------------|-----------------|---------|-----------------|---------|
| All participant visits (N=667)                         |                          |                 |         |                 |         |
| BLQ  | 56 (8%)                  | 4.1 (2.3, 7.2)  | <0.0001 | 3.4 (1.8, 6.5)  | 0.0002  |
| Quantifiable   | 611 (92%)                | 1               | REF     | 1               | REF     |
| Visits where 100% 3-day Adherence was reported (N=585) |                          |                 |         |                 |         |
| BLQ  | 28 (5%)                  | 6.8 (2.3, 20.5) | <0.0001 | 6.0 (1.8, 20.3) | 0.001   |
| Quantifiable   | 557 (95%)                | 1               | REF     | 1               | REF     |
| Visits where <100% 3-day Adherence was reported (N=82) |                          |                 |         |                 |         |
| BLQ  | 28 (34%)                 | 1.8 (0.6, 5.7)  | 0.58    | 1.3 (0.4, 4.6)  | 0.96    |
| Quantifiable   | 54 (66%)                 | 1               | REF     | 1               | REF     |

FTC-TP: emtricitabine triphosphate; BLQ: below limit of quantification; OR: odds ratio; aOR: adjusted odds ratio; 95% CI: 95% confidence interval; \*Adjusted for age, gender, race, body mass index, estimated glomerular filtration rate (eGFR), hematoctrit, CD4+ T-cell count, and ART class.

92 **EMTRICITABINE TRIPHOSPHATE IN DRIED BLOOD SPOTS PREDICTS FUTURE VIREMIA IN PWH**

Mary Morrow<sup>1</sup>, Samantha MaWhinney<sup>1</sup>, Ryan Coyle<sup>1</sup>, Stacey Coleman<sup>1</sup>, Lucas Ellison<sup>1</sup>, Jia-Hua Zheng<sup>1</sup>, Lane Bushman<sup>1</sup>, Jennifer Kiser<sup>1</sup>, Peter Anderson<sup>1</sup>, Jose R. Castillo-Mancilla<sup>1</sup>

<sup>1</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA

**Background:** The quantification of emtricitabine triphosphate (FTC-TP) in dried blood spots (DBS) is a recent adherence measure due to its 35-hour half-life in this matrix. In persons living with HIV (PWH), it is associated with viral suppression and is predictive of 3-day adherence. However, its value to predict future viremia has not been evaluated.

**Methods:** DBS, HIV viral load (VL) and self-reported (SR) adherence were prospectively obtained in a clinical cohort of PWH receiving tenofovir disoproxil fumarate (TDF)-FTC-based antiretroviral therapy (ART), using convenience sampling at regular clinic visits (up to 3 visits over 48-weeks). FTC-TP concentrations in DBS were dichotomized into quantifiable vs. below the limit of quantification (BLQ). Generalized linear logistic regression was used to estimate the odds ratio (OR) of future viremia (>20 copies/mL) based on FTC-TP concentrations at the current visit. Additional models included adjustment for tenofovir diphosphate (TFV-DP) in DBS, given its known utility as a marker of cumulative adherence, and 3-day SR adherence.

**Results:** A total of 433 PWH (69 female, 83 Black, 85 Hispanic) contributed 677 paired DBS and HIV VL samples. The OR (95% CI) for future viremia for BLQ vs. quantifiable FTC-TP in DBS was 4.1 (2.3, 7.2; p<0.0001, Table). This remained significant after adjusting for age, gender, race, body mass index, ART class, eGFR, hematoctrit and CD4+ T cell count, aOR 3.4 (1.8, 6.5; p=0.0002, Table). Including TFV-DP in the model diminished the predictive value of FTC-TP, with an aOR for BLQ vs. quantifiable FTC-TP of 1.9 (0.9, 4.1; p=0.09). However, the interaction of 3-day SR adherence with quantifiable or BLQ FTC-TP was highly informative. Among PWH who reported 100% 3-day adherence, those with BLQ FTC-TP concentrations had higher odds of future viremia vs. those with quantifiable FTC-TP, aOR 6.0 (1.8, 20.3; p=0.001, Table). In contrast, this association was not observed in PWH who reported <100% 3-day adherence, aOR 1.3 (0.4, 4.6; p=0.96, Table).

**Conclusion:** FTC-TP in DBS is a predictor of future viremia in PWH. This relationship, although diminished by including TFV-DP in the model, demonstrates the ability of a short-term adherence measure to predict future viremia. The mismatch in FTC-TP in DBS in PWH reporting 100% 3-day adherence suggests PWH who report high recent adherence, but who have an undetectable FTC-TP, could benefit from ART adherence counseling regarding their risk of future viremia.

93 **TENOFOVIR DIPHOSPHATE TO PREDICT FUTURE VIRAEMIA IN POSTPARTUM WOMEN LIVING WITH HIV**

Jasanthi Odayar<sup>1</sup>, Tamsin K. Phillips<sup>1</sup>, Nai-Chung Hu<sup>1</sup>, Siti Kabanda<sup>2</sup>, Thokozile R. Malaba<sup>1</sup>, Joanna Allerton<sup>1</sup>, Jennifer Norman<sup>1</sup>, Marvin Hsiao<sup>1</sup>, Maia Lesosky<sup>1</sup>, Landon Myer<sup>1</sup>

<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>Stellenbosch University, Cape Town, South Africa

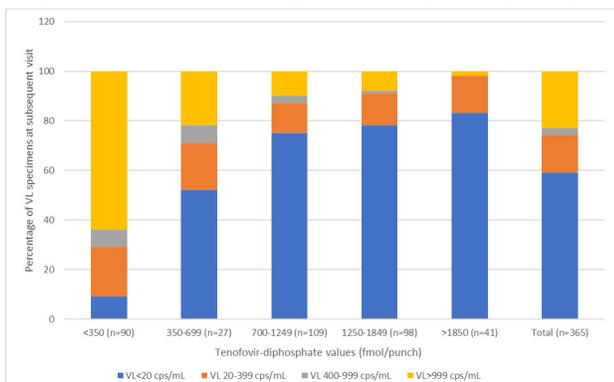
**Background:** There are few data on how tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) predicts future viral load (VL) in people living with HIV on antiretroviral therapy (ART).

**Methods:** We conducted a nested case-control study within a trial of differentiated care for postpartum ART (NCT03200054). Women were >18 years, started ART (TDF+3TC+EFV) in pregnancy and were enrolled <10w postpartum with a recent VL<400 cps/mL. Samples for VL and TFV-DP assays were taken 3-6 months over 24m. Cases were women with >1 VL>20 cps/mL and controls were a random sample of women with persistent viral suppression (VS; VL<20cps/mL). We analysed how absolute TFV-DP levels during VS predicted subsequent risk of VS; results are expressed as sensitivity (SE), specificity (SP) and test likelihood odds ratios (LORs). We also compared fluctuations in TFV-DP levels in cases (prior to elevated VL) and controls.

**Results:** Overall 81 women and 365 visits were included (median age: 29y, median time on ART: 6m; median time postpartum: 19d). The median duration between each TFV-DP and VL measure was 175d (IQR: 92-184). TFV-DP levels measured during VS were associated with risk of viraemia 3-6m later in a dose-response manner: 17% of women with TFV-DP >1850 fmol/punch had a VL>20 cps/mL at the next visit, compared to 23%, 25%, 48% and 91% of women with TFV-DP levels 1250-1849, 700-1249, 350-699 and <350 fmol/punch, respectively (Figure). Variance in TFV-DP levels during VS was significantly higher in cases vs controls (p<0.05). SE of TDF-DP >350 to predict VS at the next visit was 96% (95% CI: 93-98) and did not vary by time between measures or preceding VL values. SP of TDF-DP >350 fmol/punch to predict VS at the next visit was 54% (95% CI: 46-62) and was lower if the DBS was done <120 days before the next VL (36%, 95% CI 21-53). Adjusting for age, ART duration and time between TFV-DP and next VL measure, the LORs of VL>20 cps/mL for TDF-DP levels 1250-1849, 700-1249, 350-699 and <350 fmol/punch compared to TDF-DP>1850 fmol/punch were 1.3 (95% CI, 0.6-3.2), 1.6 (95% CI, 0.7-3.3), 3.6 (95% CI, 1.3-10.0) and 28.8 (95% CI, 9.7-85.6) respectively; the associations persisted using alternate outcome definitions (VL>400 and >1000 cps/mL).

**Conclusion:** In postpartum women, TFV-DP levels during VS predict viraemia 3-6m later, indicating the potential value of objective adherence markers in high-risk populations.

Figure: Viral load values by tenofovir-diphosphate in dried blood spot values at preceding visit



NADIA Efficacy outcomes at week 48

| Outcome  | Dolutegravir Group (N=235) | Darunavir Group (N=229) | Difference (95% CI) Percentage points | P     | Tenofovir Group (N=233) | Zidovudine Group (N=233) | Difference (95% CI) Percentage points | P     |
|--|----------------------------|-------------------------|---------------------------------------|-------|-------------------------|--------------------------|---------------------------------------|-------|
| <b>HIV-1 RNA level (primary outcome, ITT) – no (%)</b> |                            |                         |                                       |       |                         |                          |                                       |       |
| <400 copies/ml   | 212 (90.2)                 | 210 (91.7)              | -1.49 (-6.7 to 3.7)                   | 0.576 | 215 (92.3)              | 207 (89.6)               | 2.7 (-2.6 to 7.9)                     | 0.317 |
| ≥400 copies/ml   | 19 (8.1)                   | 16 (7.0)                | -                                     | -     | 14 (6.0)                | 21 (9.1)                 | -                                     | -     |
| No virological data                                    | 4 (1.7)                    | 3 (1.3)                 | -                                     | -     | 4 (1.7)                 | 3 (1.3)                  | -                                     | -     |
| Withdraw because of AE/death                           | 2 (0.8)                    | 3 (1.3)                 | -                                     | -     | 3 (1.3)                 | 2 (0.9)                  | -                                     | -     |
| Withdraw for other reasons                             | 2 (0.9)                    | 0                       | -                                     | -     | 1 (0.4)                 | 1 (0.4)                  | -                                     | -     |
| <b>HIV-1 RNA level (sensitivity analyses) – no (%)</b> |                            |                         |                                       |       |                         |                          |                                       |       |
| <400 copies/ml (adjusted)                              | 88.2                       | 89.8                    | -1.6 (-6.9 to 3.6)                    | 0.541 | 88.2                    | 85.4                     | 2.8 (-2.5 to 8.0)                     | 0.304 |
| VL <400 copies (per protocol)                          | 205 (92.3)                 | 204 (93.2)              | -0.8 (-5.6 to 4.0)                    | 0.744 | 209 (93.7)              | 200 (91.7)               | 2.0 (-2.9 to 6.8)                     | 0.423 |
| <b>Secondary and other efficacy outcomes</b>           |                            |                         |                                       |       |                         |                          |                                       |       |
| VL <1000 c/ml – no (%)                                 | 217 (92.3)                 | 213 (93.0)              | -0.7 (-5.4 to 4.1)                    | 0.781 | 219 (94.0)              | 211 (91.3)               | 2.6 (-2.1 to 7.4)                     | 0.274 |
| VL <50 c/ml – no (%)                                   | 190 (80.9)                 | 182 (79.5)              | 1.4 (-5.9 to 8.6)                     | 0.710 | 188 (80.7)              | 184 (79.7)               | 1.0 (-6.2 to 8.3)                     | 0.780 |

95 **RANDOMIZED TRIAL OF RESISTANCE TESTING FOR VIROLOGIC FAILURE IN SUB-SAHARAN AFRICA**



**Mark Siedner**<sup>1</sup>, Mahomed-Yunus Moosa<sup>2</sup>, Suzanne McCluskey<sup>1</sup>, Kevin L. Ard<sup>1</sup>, Winnie Muyindike<sup>3</sup>, Pravikrishnen Moodley<sup>2</sup>, Jaysingh Brijkumar<sup>2</sup>, Tamlyn Rautenberg<sup>4</sup>, Gavin George<sup>2</sup>, Rajesh T. Gandhi<sup>1</sup>, Brent A. Johnson<sup>5</sup>, Henry Sunpath<sup>2</sup>, Mwebesa Bwana<sup>3</sup>, Vincent Marconi<sup>6</sup>

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>University of KwaZulu-Natal, Durban, South Africa, <sup>3</sup>Mbarara University of Science and Technology, Mbarara, Uganda, <sup>4</sup>Griffith University, Brisbane, Australia, <sup>5</sup>University of Rochester, Rochester, NY, USA, <sup>6</sup>Emory University, Atlanta, GA, USA

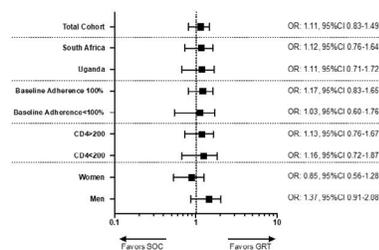
**Background:** Genotypic resistance testing (GRT) is recommended after virologic failure in resource-rich settings. By contrast, guidelines in sub-Saharan Africa promote adherence support and repeat virologic monitoring, in the absence of GRT, to guide treatment.

**Methods:** We conducted an open-label, randomized controlled trial to assess whether GRT improved virologic suppression after first-line antiretroviral therapy (ART) failure in sub-Saharan Africa. We enrolled adults in ambulatory care in South Africa and Uganda on first-line ART with an HIV-1 RNA viral load (VL)>1,000 copies/mL. We excluded those currently eligible for second-line or with prior known drug resistance. Individuals were randomized 1:1 to standard-of-care (SOC), with adherence counseling and virologic monitoring to determine management, or immediate GRT, with therapeutic decision making by clinic staff trained in GRT interpretation. The primary outcome was achievement of VL<200 copies/mL 9 months after enrollment. Analyses were intent-to-treat such that those deceased or lost from care were considered failures. Secondary outcomes included suppression less than assay, suppression while maintaining first-line ART, retention in care, mortality, and presence of drug resistance at study conclusion among those with a VL>1,000 copies/mL.

**Results:** We enrolled 840 participants, divided equally by country and sex. The median age was 37 years, median ART duration was 3 years, and 82% were taking efavirenz-based ART. There was no difference in the proportion in care and achieving a VL<200 copies/mL at 9 months by arm (SOC: 256/423, 61%; RT: 263/417, 63%, OR 1.11, 95%CI 0.83-1.49, P=0.46). Results were similar in pre-defined sub-groups (Figure). Those with a VL>1,000 copies/mL at 9 months in the SOC arm were more likely to have drug resistance detected (SOC: 75/103 75%; GRT: 46/82 56%, OR 2.39, 95%CI 1.28-4.48, P=0.01), but we found no difference in 9-month mortality (SOC: 8/423, 2%; GRT: 14/417 4%, OR 0.55, 95% 0.23-1.33, P=0.19) or other secondary outcomes.

**Conclusion:** In public clinics in sub-Saharan Africa, the addition of GRT to routine care did not improve achievement of virologic suppression 9 months after first-line ART failure but did lower the likelihood of drug resistance in those with persistent viremia. Interventions that improve management of ART failure remain elusive and are of particular importance to enable prompt transition from efavirenz-based to dolutegravir-based therapy in the region.

Figure: Forest plot demonstrating effect size and 95% confidence interval of genotypic resistance testing to improve 9 month virologic suppression in the total cohort, and by pre specified sub groups.



94 **NUCLEOSIDES AND DARUNAVIR/DOLUTEGRAVIR IN AFRICA (NADIA) TRIAL: 48 WKS PRIMARY OUTCOME**



**Nicholas Paton**<sup>1</sup>, Joseph MUSAZI<sup>2</sup>, Cissy M. Kityo<sup>3</sup>, Stephen I. Walimbwa<sup>2</sup>, Anne Hoppe<sup>2</sup>, Apolo Balyegisawa<sup>2</sup>, Arvind Kaimal<sup>2</sup>, Grace Mirembe<sup>4</sup>, James Hakim<sup>5</sup>, Henry Mugerwa<sup>3</sup>, Abraham Siika<sup>6</sup>, Barbara Castelnovo<sup>2</sup>, Agnes Kiragga<sup>2</sup>, Andrew D. Kambugu<sup>2</sup>, for the Nucleosides and Darunavir/Dolutegravir in Africa (NADIA) Trial Team

<sup>1</sup>National University of Singapore, Singapore, Singapore, <sup>2</sup>Infectious Diseases Institute, Kampala, Uganda, <sup>3</sup>Joint Clinical Research Centre, Kampala, Uganda, <sup>4</sup>Makerere University Walter Reed Project, Kampala, Uganda, <sup>5</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>6</sup>Moi University School of Medicine, Eldoret, Kenya

**Background:** WHO recommends dolutegravir with two NRTIs for second-line treatment of HIV infection after failure on an NNRTI-based regimen. There is limited evidence for efficacy of this dolutegravir regimen when prescribed NRTIs lack predicted activity due to drug resistance; or for the recommendation to switch from tenofovir to zidovudine in second-line.

**Methods:** In a two-by-two factorial, open-label, non-inferiority trial, we randomized patients failing an NNRTI/tenofovir/lamivudine first-line regimen with confirmed VL ≥1000 copies/ml to receive dolutegravir or ritonavir-boosted darunavir; and to receive tenofovir or zidovudine; all with lamivudine. Treatment was monitored by VL at 24 and 48 weeks, following WHO guidelines. Baseline NRTI resistance testing was batched, and results blinded. The primary outcome was the percentage of patients with week-48 VL <400 copies/ml using FDA snapshot algorithm (non-inferiority margin 12%).

**Results:** We enrolled 464 patients at 7 sub-Saharan African sites (61% female, 51% CD4<200, 28% VL≥100,000). At baseline, 58.5% overall had intermediate-high level resistance to tenofovir and 92% had resistance to lamivudine. Week 48 VL was <400 copies/ml in 90.2% in the dolutegravir group and 91.7% in the darunavir group (difference -1.5%; 95%CI, -6.7 to 3.7%; P=0.576; indicating non-inferiority of dolutegravir, without superiority). In the subgroup with no predicted-active NRTIs in the prescribed regimen, VL was <400 copies/ml in 92.4% of those in the dolutegravir group and 93.7% of those in the darunavir group. To date, 4 have intermediate-high level dolutegravir resistance; 0 have darunavir resistance. In the other randomized comparison, VL was <400 copies/ml in 92.3% in the tenofovir group and 89.6% in the zidovudine group (difference 2.7%; 95% CI, -2.6 to 7.9%; indicating non-inferiority of tenofovir). Grade 3/4 adverse events were uncommon and similar in frequency between groups.

**Conclusion:** Dolutegravir with two NRTIs gives highly effective viral suppression to 48 weeks, even in a patient population where many have extensive NRTI resistance and no predicted activity in prescribed NRTIs. This finding is important for patients switching from NNRTI to dolutegravir with NRTIs after known treatment failure; and for programmes switching stable patients systematically from NNRTI to dolutegravir-based regimens without VL and resistance testing. Tenofovir can be maintained in second-line therapy without switching to zidovudine, with advantages for patients and programmes.

**96 SHORT-COURSE ALENDRONATE FOR THE PREVENTION OF ART-ASSOCIATED BONE LOSS**

**Tara McGinty**<sup>1</sup>, Elena Alvarez-Barco<sup>1</sup>, Willard Tinago<sup>1</sup>, Alan Macken<sup>1</sup>, Cathal O'Brien<sup>1</sup>, Aoife G. Cotter<sup>1</sup>, Eoin Feeney<sup>1</sup>, Eoin Kavanagh<sup>2</sup>, Geraldine McCarthy<sup>2</sup>, Alan Landay<sup>3</sup>, Sam McConkey<sup>4</sup>, Peter Doran<sup>1</sup>, Patrick Mallon<sup>1</sup>, for the APART study group  
<sup>1</sup>University College Dublin, Dublin, Ireland, <sup>2</sup>Mater Misericordiae University Hospital, Dublin, Ireland, <sup>3</sup>Rush University Medical Center, Chicago, IL, USA, <sup>4</sup>Royal College of Surgeons in Ireland, Dublin, Ireland

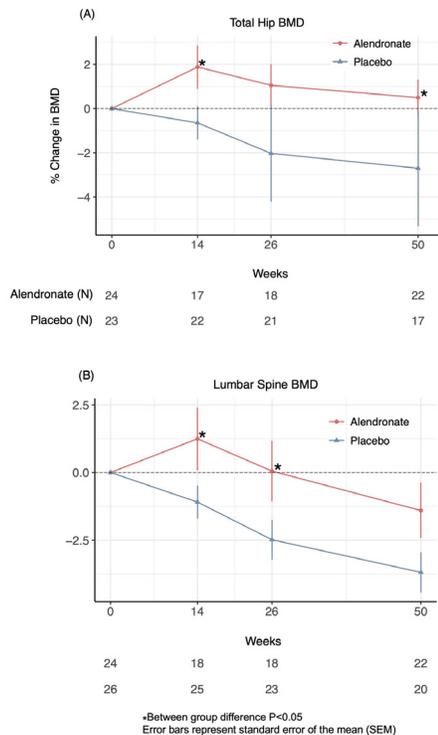
**Background:** Antiretroviral therapy (ART) initiation encompasses a period of accelerated BMD loss in people with HIV (PWH). The Alendronate for the Prevention of ART associated bone loss (APART) study aimed to evaluate if short-term use of the oral, generic bisphosphonate alendronate (ALN) could prevent BMD loss at ART initiation

**Methods:** In this multisite, double blinded, placebo-controlled phase 4 clinical trial, ART-naïve, PWH initiating ART with tenofovir disoproxil fumarate/emtricitabine and a third agent were randomized to calcium/vitamin D3 supplementation with either generic, oral ALN 70mg weekly or placebo (PL), for 2 weeks prior to ART initiation and for a total of 14 weeks. Clinical, laboratory, safety and BMD at lumbar spine (LS) and total hip (TH) were assessed at weeks 0, 14, 26 and 50. Primary endpoint was between group % change in BMD from baseline (BL) to week 50, compared using Wilcoxon rank tests. Secondary endpoints included % change from BL at weeks 14 and 26

**Results:** Of 50 subjects randomized (ALN N=24, PL N=26) 86% were male, 46% Caucasian, 34% African and 20% Hispanic, median age was 35 (32, 40) years and BMI 24 (22.3, 26.9) kg/m<sup>2</sup>. Third agent use comprised integrase inhibitors in 94% and protease inhibitors in 4%. BL BMD was not significantly different between groups. At week 50, subjects in the ALN group had a median 0.50% (-3.10, 1.80) increase in TH BMD compared to a 2.7% (-4.3, -2.05) decrease in the PL group (between group difference P=0.02, Fig 1a). At the LS, the ALN group had a 1.4% (-4.10, 3.13) loss compared to 3.69% (-4.82, -1.7) loss in the PL group (between group difference P=0.10, Fig 1b). TH BMD between-group differences were evident early at week 14 (+1.88% (-0.7, 2.81) with ALN vs -0.65% (-2.65, 1.13) with PL, P=0.036) and persisted to week 50 (Fig 1a). In contrast, at the LS, between group differences although evident at weeks 14 (+1.24% (-0.04, 3.02) with ALN vs -0.96% (-3.10, 0.78) with PL, P=0.013) and 26 (ALN +0.05% (-3.04, 3.3) vs PL -2.48% (-4.65, -0.24) , P=0.03) these didn't persist to week 50 (Fig 1b). ALN was well tolerated with no significant differences in adverse events between the groups.

**Conclusion:** In this multisite, clinical trial, 14 weeks of oral alendronate, commenced prior to ART initiation, had a sustained impact on prevention of ART-associated bone loss at the TH, while the protective effect at the LS was limited to the first 24 weeks. These data support the use of short-course, generic alendronate to preserve BMD in PWH initiating ART

**Figure 1: Percentage change from baseline in (A) total hip BMD and (B) lumbar spine BMD in those receiving Alendronate versus placebo**



**97 PREVENTION OF CARDIOVASCULAR DISEASE IN PERSONS WITH AND WITHOUT HIV**

**Michael J. Silverberg**<sup>1</sup>, Tory Levine-Hall<sup>1</sup>, Alexandra Anderson<sup>1</sup>, Stacey E. Alexeeff<sup>1</sup>, Jennifer O. Lam<sup>1</sup>, C. Bradley Hare<sup>2</sup>, Jason Flamm<sup>3</sup>, Andrew Williams<sup>4</sup>, Matthias Cavassini<sup>5</sup>, Kendall Bryant<sup>6</sup>, Michael A. Horberg<sup>7</sup>, Derek D. Satre<sup>8</sup>  
<sup>1</sup>Kaiser Permanente Northern California, Oakland, CA, USA, <sup>2</sup>Kaiser Permanente San Francisco Medical Center, San Francisco, CA, USA, <sup>3</sup>Kaiser Permanente Sacramento Medical Center, Sacramento, CA, USA, <sup>4</sup>Tufts University, Boston, MA, USA, <sup>5</sup>Lausanne University Hospital, Lausanne, Switzerland, <sup>6</sup>National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA, <sup>7</sup>Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, <sup>8</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** With higher risk of cardiovascular disease (CVD) in persons with HIV (PWH), management of hypertension, dyslipidemia, and diabetes mellitus is crucial. Here, we evaluate the extent to which PWH have successfully managed these conditions and their influence on CVD risk.

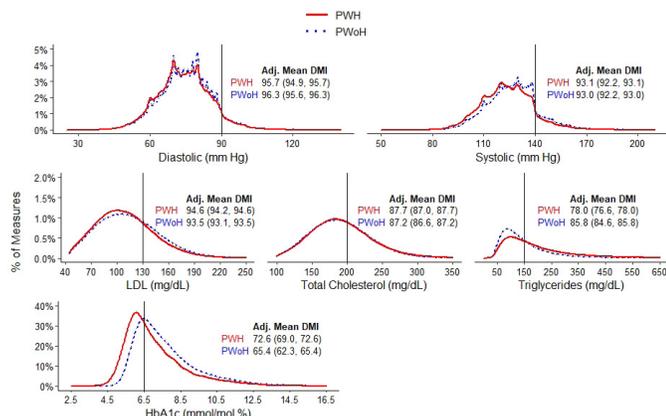
**Methods:** Cohort study of adult (≥18 years) PWH and 20:1 age-, sex-, race/ethnicity-matched persons without HIV (PWoH) who were members of an integrated healthcare system in Northern California during 2013-2017. We excluded subjects with prevalent CVD (coronary heart disease or ischemic stroke). In those with hypertension, dyslipidemia, and diabetes, we computed the disease management index (DMI), which accounts for both the amount and duration of person-time above treatment goal (vertical lines in Figure) over 6-month intervals. A DMI of 100% represents perfect control and DMI <100% is the amount in control relative to a reference treated population. Next, using Cox regression, we computed hazard ratios (HR) for incident CVD by HIV status overall, and in subgroups of those with successfully controlled risk factors (i.e., DMI 100%). Models were adjusted for other key modifiable risk factors (smoking and alcohol use), demographics, and clinical factors (Charlson comorbidity index, depression, body mass index, healthcare utilization).

**Results:** The study included 8,285 PWH and 170,517 PWoH, with similar prevalences of hypertension (19% PWH; 22% PWoH), dyslipidemia (41% for both) and diabetes (8% PWH; 9% PWoH). PWH and PWoH had similar control of most conditions (with DMIs approaching 100%) except for triglycerides (worse control for PWH) and HbA1c (better control for PWH) (Figure). Among PWH, other factors, including smoking and unhealthy alcohol use, had only marginal associations with reduced DMIs. Overall, PWH had 450 CVD events (20.8 per 1,000 person-years) and PWoH had 7,648 events (17.0 per 1,000 person-years), with an adjusted HR of 1.18 (95% CI 1.07-1.30). The elevated risk of CVD for PWH

was attenuated and not statistically significant when comparing PWH and PWOH with successfully controlled dyslipidemia (HR 1.10; 95% CI 0.91-1.34), and diabetes (HR 1.02; 0.72-1.42), but remained significant for those with successfully controlled hypertension (HR 1.35; 1.10-1.67).

**Conclusion:** Successful management of dyslipidemia and diabetes may help mitigate the CVD disparity in PWH. Further research is needed to evaluate whether more stringent hypertension treatment goals than <140/90 mm Hg are needed to prevent CVD in PWH.

Figure 1. Distribution of blood pressure, lipid, and HbA1c lab measurements



Footnote: Vertical lines represent treatment targets.

## 98 SEX MODIFIES THE ASSOCIATION BETWEEN INFLAMMATION AND VASCULAR EVENTS IN TREATED HIV

**Samuel R. Schnittman**<sup>1</sup>, Gabriele B. Beck-Engeser<sup>1</sup>, Judy K. Shigenaga<sup>1</sup>, Haelee Ahn<sup>1</sup>, Robin M. Nance<sup>2</sup>, Vanessa York<sup>1</sup>, Joseph A. Delaney<sup>3</sup>, Susan Heckbert<sup>2</sup>, David Tirschwell<sup>2</sup>, Felicia C. Chow<sup>1</sup>, Fran Aweeka<sup>1</sup>, Carl Grunfeld<sup>1</sup>, Heidi Crane<sup>2</sup>, Peter W. Hunt<sup>1</sup>, for the CFAR Network of Integrated Clinical Systems (CNICS) Network

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>University of Manitoba, Winnipeg, Canada

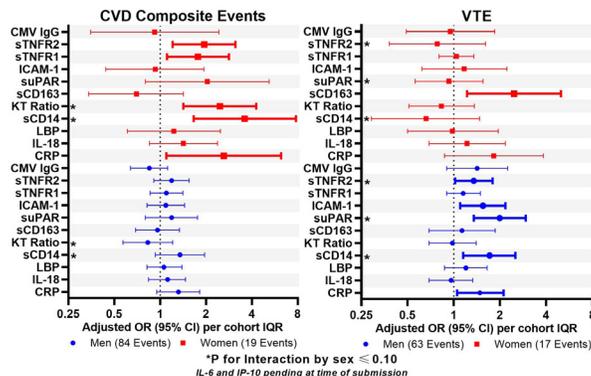
**Background:** Inflammation persists in people with HIV (PWH) despite antiretroviral therapy (ART) and predicts morbidity and mortality. The specific inflammatory pathways associated with myocardial infarction (MI), ischemic stroke, and venous thromboembolism (VTE), and whether these pathways are modified by sex, have yet to be fully described.

**Methods:** Using a case-cohort design, we randomly sampled all CNICS participants with available plasma after 1 year of ART-mediated viral suppression (the cohort), and from the same timepoint, all participants who were subsequently diagnosed with an incident type 1 or 2 MI (T1MI, T2MI), ischemic stroke, or VTE (all centrally adjudicated). Composite cardiovascular disease (CVD) event included T1MI and ischemic stroke. The relationship between 11 plasma biomarkers normalized to the cohort interquartile range (IQR) and subsequent event risk was assessed by logistic regression, adjusting for age, natal sex, nadir CD4, and other potential confounders (smoking, IDU, ASCVD risk score, and HCV history).

**Results:** We sampled a random sub-cohort of 979 (of 9430 eligible) participants and 103 CVD (75 T1MI, 30 ischemic stroke), 56 T2MI, and 80 VTE cases. In the sub-cohort, median age was 47, 82% were men, and 17% had a history of IDU. Median ASCVD risk was 4% and median current and nadir CD4 were 576 and 248, respectively. After adjustment, women had a 1.4-2.5 fold IQR higher CRP, LBP, sCD14, suPAR, ICAM-1, and CMV IgG than men ( $P < 0.03$  for all). Higher CRP, sCD14, and sTNFR2 were associated with subsequent T1MI (1.3-1.6 fold higher odds per IQR increase,  $P < 0.01$  for all), while higher CRP, suPAR, and ICAM-1 were associated with VTE (1.5-1.7 fold higher odds per IQR increase,  $P < 0.01$  for all). All biomarkers except CRP, LBP, and CMV IgG were associated with incident T2MI (1.4-2.8 fold greater odds per IQR increase,  $P < 0.001$  for all). Inflammatory markers tended to be associated with CVD events more strongly among women compared to men (KT ratio and sCD14  $P$  for interaction = 0.005 and 0.08) but tended to be associated with VTE events more strongly in men than women (sCD14 and sTNFR2  $P$  for interaction = 0.02 and 0.10).

**Conclusion:** Discrete pathways of inflammation independently predict CVD and VTE events in treated HIV, and many of these pathways are modified by sex. As inflammation predicts CVD events more strongly in women than in men,

representation of women in clinical studies of immune-based interventions in treated HIV infection is critical.



99

## IDENTIFICATION OF UNIQUE PROTEINS PREDICTIVE OF MORTALITY AND MECHANISMS IN HIV

**Priscilla Hsue**<sup>1</sup>, Peter Ganz<sup>2</sup>, Mark Segal<sup>1</sup>, Janet P. Tate<sup>2</sup>, Hilary A. Tindle<sup>3</sup>, Kaku So-Armah<sup>4</sup>, Amy Justice<sup>2</sup>, Matthew Freiberg<sup>3</sup>

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>Yale University, New Haven, CT, USA, <sup>3</sup>Vanderbilt University, Nashville, TN, USA, <sup>4</sup>Boston University, Boston, MA, USA

**Background:** Risk prediction tools in HIV are limited by their focus on known pathways. In contrast, proteins orchestrate human biology in health and in disease and be used to individualize risk assessment as well as identify new potential therapeutic targets. We thus applied large-scale proteomics to: (i) identify new biomarkers that can inform disease biology and (ii) develop proteomic risk models predictive of all-cause mortality among HIV+ individuals.

**Methods:** The Veterans Aging Cohort Study Biomarkers Cohort (VACS BC) is a longitudinal cohort of veterans with and without HIV. We measured plasma levels of 4926 proteins in all 1524 HIV+ VACS BC participants using aptamers (SOMAscan<sup>®</sup> assay). Univariate associations of proteins with mortality were assessed by Cox proportional hazards and attendant p-values and q-values (false discovery rates; FDR). Multivariate modeling of mortality based on proteins, both with and without adjustment for clinical, demographic and biomarker variables, was performed using the elastic net. The VACS BC cohort analysis was divided into derivation (80%) and validation (20%) datasets.

**Results:** We analyzed plasma samples of 1524 HIV+ veterans collected in 2005-2006. The average age was 52 years, 97% were male, the median CD4 count was 399 cells/mm<sup>3</sup>, and 66% had an undetectable viral load. From 2005 to 2019 (median follow-up 8.9 years), there were 421 mortality events. At an FDR of 5%, 48% of proteins were associated with mortality outcomes. The log<sub>2</sub> hazard ratios (HRs) and levels of significance for the top 10 prognostic proteins are listed in the Table below. In the construction of the risk model via cross-validation, the elastic net (with the 1 standard error rule) selected 9 prognostic proteins: GNPTG, SVEP1, WFDC2, ADAMTSL1, EGFR, PROC, SET, SPON2 and EFEMP1. The c-statistic for the 9-protein model was 0.72 in the derivation set and 0.71 in the validation set, results not meaningfully altered by allowing for inclusion of CD4, nadir CD4 count, HIV RNA levels, age, and VACS score.

**Conclusion:** Using large-scale proteomics, we identified numerous unique proteins predictive of mortality in HIV. A risk score based on 9 proteins provided moderately good discriminative accuracy, despite heterogeneous causes of death in this population; furthermore, this protein risk score was more predictive than direct measures of HIV infection or age. The large number of prognostic proteins identified will serve as the basis of future pathway and network analyses to inform the bio

| Gene Name | HR   | p-value  | q-value  | Protein Name   |
|-----------|------|----------|----------|--|
| GNPTG     | 1.29 | 5.54E-36 | 8.25E-33 | N-acetylglucosamine-1-phosphotransferase subunit gamma           |
| SVEP1     | 1.39 | 6.22E-36 | 8.25E-33 | Sushi, vWF type A, EGF and pentraxin domain-containing protein 1 |
| ADAMTSL2  | 1.34 | 1.56E-33 | 1.38E-30 | ADAMTS-like protein 2  |
| SVEP12    | 1.37 | 1.72E-32 | 1.14E-29 | Sushi, vWF type A, EGF and pentraxin domain-containing protein 1 |
| SPON2     | 1.57 | 3.50E-32 | 1.85E-29 | Spondin-2  |
| EFEMP1    | 1.26 | 7.80E-32 | 3.45E-29 | EGF Containing Fibulin Extracellular Matrix Protein 1            |
| EGFR      | 0.50 | 2.07E-31 | 7.84E-29 | Epidermal growth factor receptor                                 |
| FSTL3     | 1.37 | 1.32E-30 | 4.39E-28 | Follistatin-like 3   |
| ADAMTSL1  | 1.65 | 3.66E-29 | 1.08E-26 | ADAMTS protein 1   |
| SET       | 0.51 | 5.43E-29 | 1.44E-26 | SET protein  |

Table: Top Ten Prognostic Proteins for Mortality Among HIV-infected individuals in VACS

**100 BIOLOGICAL PROFILES PREDICT CORONARY ARTERY DISEASE IN PWH AND RISK-MATCHED CONTROLS**

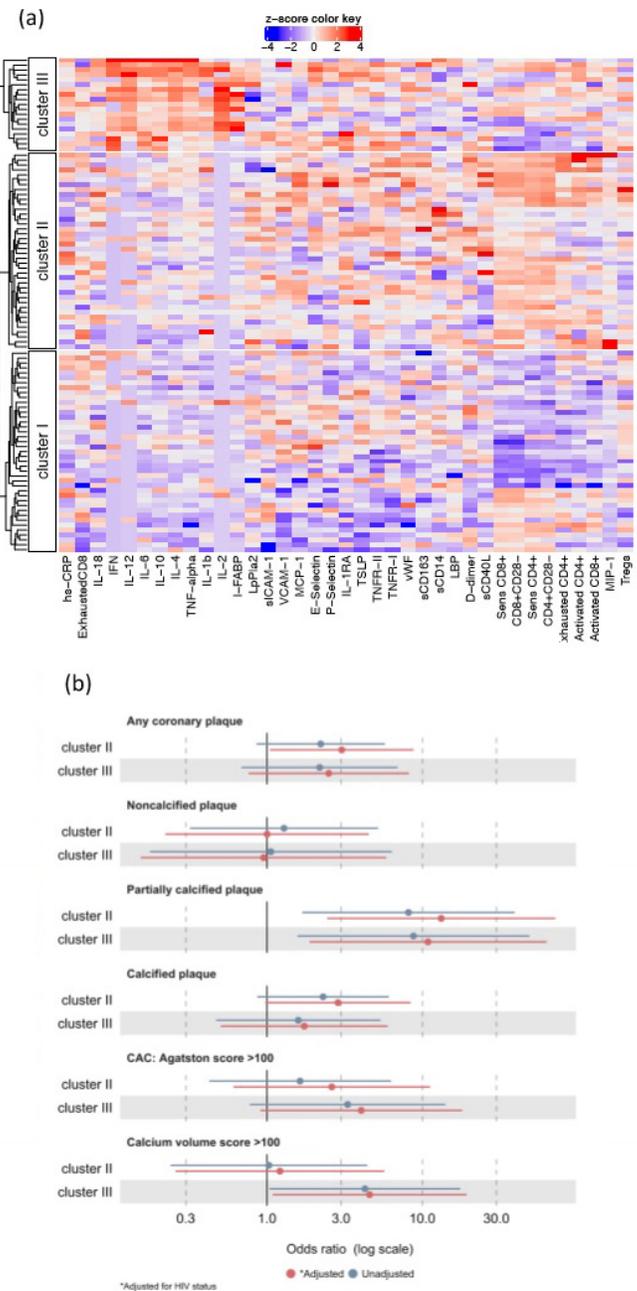
**Padraig McGettrick**<sup>1</sup>, Willard Tinago<sup>1</sup>, Alejandro Garcia-Leon<sup>1</sup>, Julie O'Brien<sup>2</sup>, Niall Mahon<sup>3</sup>, Leo Lawler<sup>3</sup>, Aoife G. Cotter<sup>1</sup>, John S. Lambert<sup>1</sup>, Gerard Sheehan<sup>2</sup>, Alan Landay<sup>4</sup>, Caroline Sabin<sup>5</sup>, Patrick Mallon<sup>1</sup>  
<sup>1</sup>University College Dublin, Dublin, Ireland, <sup>2</sup>University Hospital Limerick, Limerick, Ireland, <sup>3</sup>Mater Misericordiae University Hospital, Dublin, Ireland, <sup>4</sup>Rush University, Chicago, IL, USA, <sup>5</sup>University College London, London, UK

**Background:** Inflammation has been implicated in the increased risk of coronary artery disease (CAD) observed in individuals with HIV (PWH) with the immune or inflammatory pathways contributing to CAD not well defined.

**Methods:** The HIV UPBEAT CAD sub-study enrolled PWH >40 years old on effective antiretroviral therapy (ART) and uninfected controls propensity matched for CAD risk. We used coronary computed tomography angiography (CCTA) to estimate subclinical CAD and performed chemiluminescence immunoassays to evaluate 28 biomarkers of systemic, innate and vascular inflammation and 10 T-cell immune markers by flow cytometry. Principal component (PC) analysis was used to reduce data dimensionality followed by PC-based unsupervised hierarchical clustering to partition participants into biomarker-derived clusters. Associations between clusters and subclinical CAD were explored using logistic regression with additional adjustment for HIV status. Data are median (interquartile range) unless specified.

**Results:** Of 101 participants (51% PWH), 72% were male, 75% Caucasian and median age 49 (45, 55) years. 35.6% had subclinical CAD (32% of PWH). We identified three clusters (figure 1a): Cluster 1 (n=41, 32% PWH) characterised by lower T-cell senescence and activation and lower TNF, TNF R1/2 and IL1ra; Cluster 2 (n=40, 72% PWH) characterised by higher T-cell senescence and exhaustion (higher T-cell senescence, activation, effector T cells, higher TNFR1/2, MIP, but lower IL2, IL12 and IFN); and Cluster 3 (n=19, 52% PWH) characterised by higher inflammation (higher IL2, IL12, IFN, IL4, IL10, TNF, IL6, IL1b, IL1ra, IFABP). With the exception of HIV status, baseline demographics were similar between clusters including CD4+ T-cell count and CD4+CD8+ ratio for PWH. Compared to those in Cluster 1, those in Cluster 2 and 3 had greater presence of any coronary plaque, partially calcified and calcified plaque, an association which for cluster 2 strengthened after adjustment for HIV status (figure 1b). In contrast, participants in Cluster 3 had higher calcification scores [Agatston score >100, Calcium volume score >100] which persisted in adjusted analyses.

**Conclusion:** In a cohort of CAD risk-matched individuals with and without HIV, we identified two clusters associated with distinct characteristics of subclinical CAD, one characterised by T cell senescence and exhaustion, the other by systemic inflammation. Biological phenotyping may help better predict those at risk of long term comorbidities common in ART treated PWH.



**Figure 1: (a) Characterization of biomarker derived clusters and (b) relationship with subclinical Cardiovascular disease**

**101 12-YEAR COGNITIVE DECLINE IS ASSOCIATED WITH LUNG DISEASE, DIABETES, AND DEPRESSION**

**Scott Letendre**<sup>1</sup>, Ronald J. Ellis<sup>1</sup>, Bin Tang<sup>1</sup>, Donald Franklin<sup>1</sup>, Ned Sacktor<sup>2</sup>, Leah Rubin<sup>2</sup>, Susan Morgello<sup>3</sup>, J. Allen McCutchan<sup>1</sup>, Christina M. Marra<sup>4</sup>, Benjamin B. Gelman<sup>5</sup>, Ann C. Collier<sup>6</sup>, David Clifford<sup>6</sup>, Robert K. Heaton<sup>1</sup>  
<sup>1</sup>University of California San Diego, San Diego, CA, USA, <sup>2</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>4</sup>University of Washington, Seattle, WA, USA, <sup>5</sup>University of Texas at Galveston, Galveston, TX, USA, <sup>6</sup>Washington University in St Louis, St Louis, MO, USA

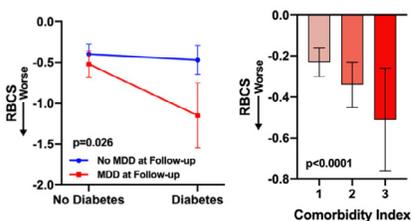
**Background:** Cognitive impairment is more common in people with HIV (PWH) than in the general population and is associated with worse quality of life and worse health outcomes. Most studies of cognitive change in PWH have focused on decline over a few years but no projects have assessed cognitive change and its correlates over more than a decade. To address this key gap, the 6-site,

U.S. CHARTER project reassessed 397 participants 12 years after their initial assessment.

**Methods:** Standardized, comprehensive neuromedical and neurocognitive assessments were performed at the initial and 12-year timepoints and included a neuropsychological test battery that assessed 7 cognitive domains as well as medical history, prescribed medications, drug use, and blood collection. The outcome was regression-based change score (RBCS), which was calculated using normative data from people without HIV. Decline was defined as change worse than the 5th percentile of the normative data. Demographic, disease, drug use, and therapy characteristics were analyzed using multivariable regression with  $\alpha=0.20$  for covariate inclusion.

**Results:** At the 12-year visit, mean age was 56 (range 33-81), 23% were women, 58% had race/ethnicity other than white, and 96% took antiretroviral therapy (ART, mean 15.3 years) with mean CD4+ T-cell count 607/ $\mu$ L and plasma HIV RNA  $\leq 200$  cp/mL in 90%. The criterion for cognitive decline was met in 23.4%. In the best model, worse RBCS was associated with chronic lung disease ( $p=0.002$ ) and lifetime cannabis use disorder ( $p=0.037$ ) (model  $p<0.0001$ ). The model also included an interaction between diabetes and major depressive disorder (MDD) ( $p=0.026$ ): people with diabetes and MDD had worse cognitive decline than people with diabetes without MDD or people with neither condition. Hypertension also entered some models and a comorbidity index that combined it with diabetes and chronic lung disease was incrementally associated with decline ( $p<0.0001$ ).

**Conclusion:** Nearly a quarter of treated PWH experienced cognitive decline over 12 years and worse change was associated with previously reported aging-related risk factors (e.g., diabetes) but also with other risk factors that have not been reported (chronic lung disease, MDD, cannabis use disorder). The CHARTER cohort was intended to reflect PWH who receive outpatient healthcare in the U.S. when it was first recruited but these 12-year findings may be affected by survivor bias and selection bias.

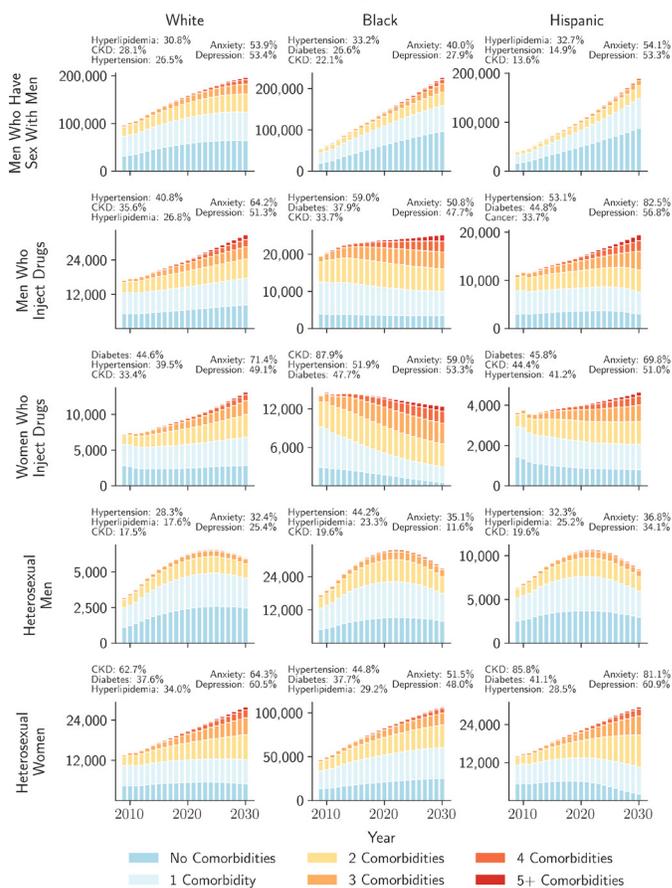


with men [MSM], injection drug use [IDU], and heterosexual contact) to year 2030.

**Results:** Accompanying an increase in median age of PWH (50 to 53 years), the projected prevalence of multimorbidity increased from 2020 to 2030 overall (from 30.3% to 34.7%) and among all 15 key-populations (Figure). Racial disparities expand over time, with the highest and lowest multimorbidity burden projected among Black IDU women (74.7%) and Hispanic MSM (20.9%) in 2030. Hispanic heterosexual women experienced the largest multimorbidity burden increase (absolute difference=23.5%), while multimorbidity burden reduced slightly among White and Black heterosexual men (<math><2\%</math> change). Anxiety (mean prevalence [range]= 0.54 [0.12–0.82]) and depression (0.49 [0.26–0.64]) were among the most prevalent comorbidities across all key-populations in 2030, followed by hypertension (0.38 [0.15–0.59]), CKD (0.36 [0.13–0.88]) and diabetes (0.31 [0.11–0.48]).

**Conclusion:** The prevalence of multimorbidity in PWH is projected to increase over the next decade. The most prevalent comorbidities, particularly anxiety, depression, hypertension, CKD, and diabetes, differ by race/ethnicity, sex, and transmission category. Focusing on the most burdensome comorbidities in each key-population can help with the long-term care and life-expectancy of PWH.

**Figure:** Projected burden of multimorbidity among people with HIV using ART in the United States, 2009-2030. Panels show the number of prevalent physical comorbidities (y-axis) over time (x-axis) in 15 key-populations by race/ethnicity, sex, and transmission group. Top legends show the comorbidity prevalence in year 2030 for each subgroup, with the top three physical comorbidities shown on the left and the two mental comorbidities shown on the right. The model is calibrated to NA-ACCORD data from 2010 to 2017 and projections are made from 2018 to 2030.



102 MULTIMORBIDITY IN PEOPLE WITH HIV USING ART IN THE US: PROJECTIONS TO 2030

Parastu Kasaie<sup>1</sup>, Cameron Stewart<sup>1</sup>, Elizabeth Humes<sup>1</sup>, Lucas Gerace<sup>1</sup>, Kelly Gebo<sup>2</sup>, Cynthia Boyd<sup>2</sup>, Amy Justice<sup>3</sup>, Peter Zandi<sup>2</sup>, Richard Moore<sup>2</sup>, Kate Buchacz<sup>4</sup>, Viviane D. Lima<sup>5</sup>, Amanda Willig<sup>6</sup>, Chrise Wong<sup>1</sup>, Keri N. Althoff<sup>1</sup>, for the Projecting Age, multimorbidity, and polypharmacy (PEARL) model and the North American AIDS Cohort

<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Yale University, New Haven, CT, USA, <sup>4</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>5</sup>University of British Columbia, Vancouver, Canada, <sup>6</sup>University of Alabama at Birmingham, Birmingham, AL, USA

**Background:** As people with HIV (PWH) receiving antiretroviral therapy (ART) age, the projected burden and racial disparities of age-related comorbidities among key-populations remain uncertain.

**Methods:** ProjEcting Age, MultiMorbidity, and Polypharmacy (PEARL) is an agent-based simulation of HIV and comorbidities among PWH receiving ART in the US (2009–2030). PEARL assesses nine major mental/physical comorbidities, including depression and anxiety, treated hypertension, diabetes, hyperlipidemia, chronic kidney disease (CKD), cancer, myocardial infarction (MI), and end-stage liver disease (ESLD). These are modeled in the presence/absence of three underlying risk-factors, including smoking, Hepatitis C virus (HCV) infection, and body mass index (BMI) change 2-year post-ART. Future comorbidity incidence is estimated at an individual-level from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Our objective was to project multimorbidity (2+ physical comorbidities) burden among 15 key-populations in the US defined by race/ethnicity (White, Black, and Hispanic), sex (male, female), and acquisition risk group (men who have sex

**103 COVID-19 HOSPITALIZATION AMONG PEOPLE WITH HIV OR SOLID ORGAN TRANSPLANT IN THE US**

**Jing Sun**<sup>1</sup>, Rena Patel<sup>2</sup>, Vithal Madhira<sup>3</sup>, Amy L. Olex<sup>4</sup>, Evan French<sup>4</sup>, Jessica Y. Islam<sup>5</sup>, Richard Moffitt<sup>6</sup>, Nora Franceschini<sup>5</sup>, Roslyn B. Mannon<sup>7</sup>, Gregory D. Kirk<sup>1</sup>, for the National COVID Cohort Collaborative  
<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>Palila Software, Reno, NV, USA, <sup>4</sup>Virginia Commonwealth University, Richmond, VA, USA, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>Stony Brook University, Stony Brook, NY, USA, <sup>7</sup>Nebraska Medical Center, Omaha, NE, USA

**Background:** The role of immunosuppression/compromise (ISC) in risk of severe COVID-19 is unknown. While ISC could reduce control of SARS-CoV-2 viremia, it might also dampen the severe immune response to the virus; data comparing ISC groups is limited.

**Methods:** Using patient-level data from 34 sites in the U.S. National COVID Cohort Collaborative (N3C), we compared risk of COVID-19 hospitalization amongst COVID-19 patients in 3 ISC groups (1,300 persons with HIV [PWH]; 2,142 solid organ transplant [SOT] patients; 41 PWH with SOT) to 288,743 COVID-19 patients without HIV or SOT (HIV-/SOT-). COVID-19+ was defined by RT-PCR, antibody test, or diagnostic codes. HIV infection, SOT and comorbidities were defined by conditions/diagnostic codes within 2 years prior to first COVID-19+. Hospitalization was defined by inpatient care between 14 days prior to 45 days after the first COVID-19+. Odds ratios of hospitalization were estimated using multivariable logistic regression models adjusting for demographics, study site, and comorbidities (severe liver disease, diabetes, cancer, kidney disease, and total comorbidities [0, 1, 2, ≥3]).

**Results:** Of 292,226 COVID-19+ patients, the median age was 41 years (IQR: 25-58), 46% male, 47% non-Hispanic white (NHW), and 17% non-Hispanic black (NHB). PWH and SOT patients, respectively, were more likely to be older (median: 50 & 56), male (70% & 60%), and had ≥ 3 comorbidities than overall N3C patients (30% & 64% vs. 8%). PWH were more likely to be NHB (50%) and SOT patients were more likely to be NHW (41%). Overall, 26% of HIV-/SOT- COVID-19 patients were hospitalized. In crude analyses with HIV-/SOT- as the referent group (Table), COVID-19 patients with HIV, SOT or both had a 2.3, 4.4, or 6.9-fold increased odds of hospitalization, respectively. After adjustment for demographics and site, the risk was attenuated but remained statistically significant (Model a). Sequential adjustment for the type and number of comorbidities obviated the estimated risk among PWH, while SOT patients had persistently increased odds of hospitalization (Model b).

**Conclusion:** ISC patients (PWH and SOT) are more likely to be hospitalized with COVID-19 independent of demographics. However, this increased hospitalization risk was driven mainly by the high burden of comorbidities in both groups. Only SOT patients had an independent risk of hospitalization after adjusting for comorbidities. Ongoing analyses will examine the impact of ISC on additional COVID-19 outcomes (i.e. ventilation use, death).

**Table. Odds of hospitalization with COVID-19 for people with HIV, solid organ transplant or both compared to N3C patients in crude and adjusted models.**

| Immunosuppression groups | Crude estimates   |         | Adjusted estimates <sup>a</sup> |         | Adjusted estimates <sup>b</sup> |         |
|--------------------------|-------------------|---------|---------------------------------|---------|---------------------------------|---------|
|                          | OR (95% CI)       | P-value | OR (95% CI)                     | P-value | OR (95% CI)                     | P-value |
| HIV- & SOT- (N=288,743)  | Ref.              | Ref.    | Ref.                            | Ref.    | Ref.                            | Ref.    |
| PWH (N=1,300)            | 2.30 (2.06-2.56)  | <0.01   | 1.4 (1.24, 1.58)                | <0.01   | 1.1 (0.97-1.25)                 | 0.12    |
| SOT (N=2,142)            | 4.38 (4.01-4.78)  | <0.01   | 3.04 (2.77-3.35)                | <0.01   | 1.70 (1.54-1.89)                | <0.01   |
| HIV+ & SOT+ (N=41)       | 6.87 (3.50-13.47) | <0.01   | 3.03 (1.48-6.20)                | <0.01   | 1.60 (0.77-3.31)                | 0.20    |

<sup>a</sup>Model adjusted for age, sex, race and ethnicity (Black non-Hispanic, white Hispanic, white non-Hispanic, others), and study site.

<sup>b</sup>Model adjusted for age, sex, race and ethnicity (Black non-Hispanic, white Hispanic, white non-Hispanic, others), study site, severe liver disease, diabetes, cancer, renal disease, and total number of comorbidities (0, 1, 2, 3).

HIV- & SOT-: people without HIV or solid organ transplant; PWH: people with HIV; SOT: solid organ transplant patient; HIV+ & SOT+: PWH had solid organ transplant; OR: odds ratio; 95% CI: 95% confidence interval.

**104 DISPARITIES IN TIMELY RECEIPT OF ART PRESCRIPTION IN HIV CARE IN THE US, 2012-2018**

**Jun Li**<sup>1</sup>, Elizabeth Humes<sup>2</sup>, David B. Hanna<sup>3</sup>, Jennifer S. Lee<sup>2</sup>, Keri N. Althoff<sup>1</sup>, Richard Moore<sup>2</sup>, Heidi Crane<sup>4</sup>, Jonathan Colasanti<sup>5</sup>, Michael A. Horberg<sup>6</sup>, Ank Nijhawan<sup>7</sup>, Gypsyamber D'Souza<sup>2</sup>, Christopher T. Rentsch<sup>8</sup>, Kelly Gebbo<sup>2</sup>, Kate Buchacz<sup>1</sup>, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

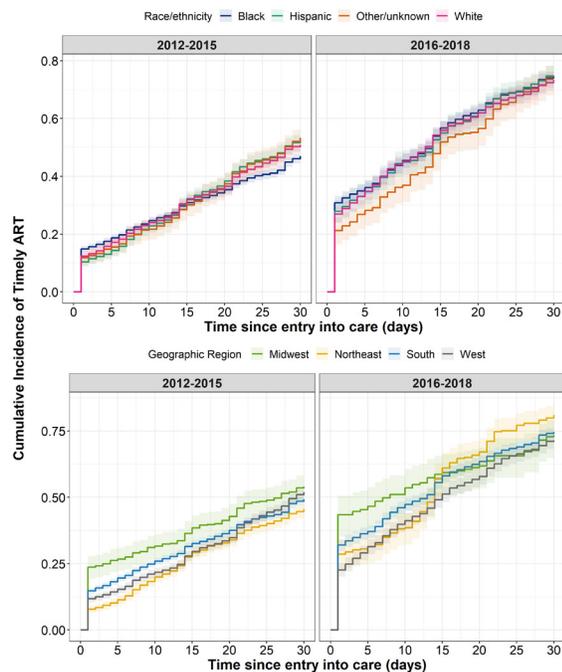
<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>3</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>4</sup>University of Washington, Seattle, WA, USA, <sup>5</sup>Emory Center for AIDS Research, Atlanta, GA, USA, <sup>6</sup>Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, <sup>7</sup>University of Texas Southwestern, Dallas, TX, USA, <sup>8</sup>VA Connecticut Healthcare System, West Haven, CT, USA

**Background:** Since 2012, the U.S. Department of Health and Human Services (DHHS) has recommended ART for all people with HIV (PWH) regardless of CD4 count. We studied trends in and sociodemographic and clinical disparities in timely receipt of ART prescription (ART) from 2012–2018.

**Methods:** We examined HIV treatment-naïve adults who newly presented to HIV care (i.e., HIV viral load [VL] >500 copies/mL and no clinical AIDS diagnosis >30 days prior to entry into care) at 13 U.S. NA-ACCORD clinical cohorts who had a recorded CD4 at presentation during 2012–2018. We calculated cumulative incidence of timely ART (within 30 days of entry into care) using the Kaplan-Meier survival function by year of entry into care, with additional stratifications by the period of entry into care (2012-2015 vs. 2016-2018) and by race/ethnicity or geographic region. Discrete time-to-event models were fit to assess trends in timely ART by calendar year adjusted for age, sex, risk group, race/ethnicity, geographic region, AIDS diagnosis, history of alcohol or drug dependence/abuse, mental health diagnoses, and CD4 and VL at presentation, overall and stratified by the period of entry into care.

**Results:** Among 11,853 eligible treatment-naïve PWH, 48% were men who had sex with men, 14% were women, 45% Black, 15% Hispanic/Latino, 32% aged 18-29, and 7% aged ≥60 years. Cumulative incidence of timely ART increased from 42% in 2012 to 82% in 2018, with gains across race/ethnic groups and regions (Figure). In the multivariable model for 2012-2018, lower rates of timely ART were seen in Black than White PWH (adjusted hazard ratio [aHR] 0.89, 95% confidence interval [CI] 0.83–0.94), PWH living in the South than the West (aHR 0.78, CI 0.69–0.88), and PWH with a history of drug dependence/abuse diagnosis (aHR 0.81, CI 0.74–0.90). In the models for the 2016-2018 period, Black PWH (aHR 0.92, CI 0.83–1.02) and PWH in the South (aHR 0.97, CI 0.75–1.26) no longer had significantly lower rates of timely ART, but PWH in the Northeast had higher rates (aHR 1.37, CI 0.99–1.90) than PWH in the West region; drug dependence/abuse history remained associated with delayed ART (aHR 0.72, CI 0.61–0.85).

**Conclusion:** Timely ART has substantially improved in the United States since the release of DHHS universal treatment guidelines. Although race/ethnic and some geographic disparities in timely ART lessened, PWH with drug dependence/abuse diagnosis still had deficits, suggesting the need for additional support services for this population.



### 105 GEOGRAPHIC DIFFERENCES IN TIME TO VIRAL SUPPRESSION IN THE DEEP SOUTH, 2012-2019

Aadia Rana<sup>1</sup>, David S. Batey<sup>1</sup>, John Bassler<sup>1</sup>, Ariann Nassel<sup>1</sup>, Lauren Ostrenga<sup>2</sup>, Debbie Wendell<sup>3</sup>, Danita Crear<sup>3</sup>, Xueyuan Wang<sup>4</sup>, Melverta Bender<sup>4</sup>, Emma Kay<sup>1</sup>, Mariel Parman<sup>1</sup>, Emily Levitan<sup>1</sup>, Michael Mugavero<sup>1</sup>

<sup>1</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>2</sup>Louisiana Department of Health, New Orleans, LA, USA, <sup>3</sup>Alabama Department of Public Health, Montgomery, AL, USA, <sup>4</sup>Mississippi Department of Health, Jackson, MS, USA

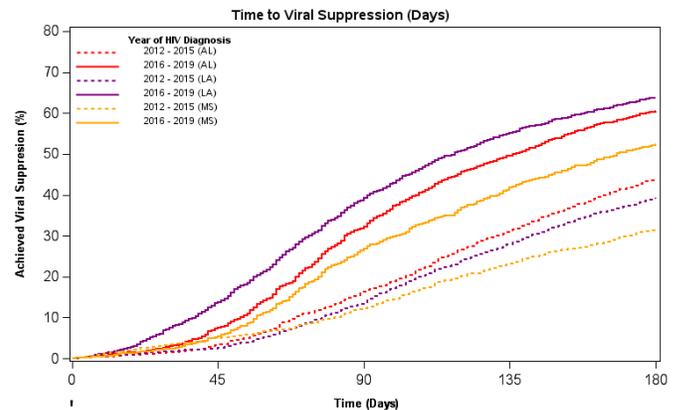
**Background:** As outlined in the United States (US) Ending the HIV Epidemic initiative, achieving early and sustained viral suppression (VS) following diagnosis of HIV infection is critical to improving outcomes and reducing transmission. Dramatic geographic variability in time from HIV diagnosis to VS exists within the US including the Deep South, a region disproportionately affected by the domestic epidemic. Understanding drivers of this heterogeneity is essential to inform individual and population health approaches to ending the epidemic.

**Methods:** We conducted a retrospective, population-based cohort study of all persons  $\geq 13$  years with newly diagnosed HIV from 2012-2019 in Alabama (AL), Louisiana (LA), and Mississippi (MS), using data collected in the Enhanced HIV/AIDS Reporting System (eHARS), a standardized document-based surveillance database used by all state health departments to report to the National HIV Surveillance System. We used the Kaplan-Meier Method to describe time to viral suppression by year of diagnosis, and conducted meta-analysis of state specific Cox Proportional Hazards models to examine associations with age, race/ethnicity, gender at birth, mode of HIV transmission, and AIDS Stage at diagnosis.

**Results:** The median time in days to VS (95% CI) in AL (n=2547), LA (n=4371), and MS (n=1876) in 2012-2015 was 211.0 (199.0-225.0), 242.0 (230.0-253.0), and 332.0 (308.0-365.0), respectively; this drastically improved in all states during 2016-2019 (AL n=2311, LA n=3845, MS n=1479) to 137.0 (129.0-144.0), 118.0 (112.0-123.0), and 168.0 (160.0-181.0) days (Figure 1). Adolescent age 13-24 years [Hazard Ratio (HR): 0.845 (95% CI 0.806, 0.885), ref age  $\geq 45$ ], male gender at birth [HR: 0.846 (0.815, 0.878) ref female], and heterosexual transmission [HR 0.898 (0.896, 0.899), ref: men who have sex with men] were associated with longer time to VS; while Stage 3, AIDS at diagnosis [HR 1.385 (1.332, 1.441), ref: non-Stage 3] was associated with shorter time to VS.

**Conclusion:** Overall trends in time to VS are improving in AL, LA, and MS which may reflect changing guidelines recommending universal test and treat strategies and better tolerated treatment regimens. A significant change in earlier time to VS in LA may be related to additional interventions including Medicaid expansion in 2016. We will next use geospatial analytic tools to assess

the impact and interplay of individual, structural, and community level socio-contextual variables on time to VS in these areas of the Deep South.



### 106 DECREASED HIV DIAGNOSES AMONG MSM OF COLOR IN THRIVE-FUNDED JURISDICTIONS, 2014-2018

Kashif Iqbal<sup>1</sup>, Xueyuan Dong<sup>2</sup>, Weiming Zhu<sup>1</sup>, Kenneth L. Dominguez<sup>1</sup>, Mary Tanner<sup>1</sup>, Athena Kourtis<sup>1</sup>, Sonia Singh<sup>1</sup>, Karen W. Hoover<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>ICF International, Atlanta, GA, USA

**Background:** While the total number of HIV diagnoses decreased in the United States from 2014-2018, diagnoses increased among young men who have sex with men (MSM) of color. THRIVE was a demonstration project that funded 7 health departments from 2015-2020 to develop community collaboratives to provide comprehensive HIV prevention and care services for MSM of color. Twenty-eight Metropolitan Statistical Area (MSA) jurisdictions were eligible for THRIVE funding because they had the highest rates of HIV diagnoses among Black/African American (Black) MSM and/or Hispanic/Latino MSM in 2014. This study evaluated trends in HIV diagnoses among MSM in jurisdictions awarded THRIVE funding compared to jurisdictions eligible for THRIVE but not awarded funding.

**Methods:** Data from the National HIV Surveillance System were analyzed to determine the number of HIV diagnoses from 2014-2018 among White, Black, and Hispanic/Latino MSM for: 1) 7 THRIVE-eligible jurisdictions that were awarded THRIVE funding, 2) 11 THRIVE-eligible jurisdictions that were not awarded THRIVE funding, and 3) and overall for United States and Puerto Rico. The Estimated Annual Percent Change (EAPC) and 95% confidence interval (CI) were used to evaluate trends for each of the three groups stratified by age group and race/ethnicity.

**Results:** From 2014-2018, 130,508 MSM were diagnosed with HIV infection in the U.S.; 8.4% were in THRIVE jurisdictions and 26% in unfunded THRIVE-eligible jurisdictions. During 2014-2018 in THRIVE jurisdictions, HIV diagnoses significantly decreased among Black MSM (EAPC -4.4 [95% CI -6.0, -2.7]) and White MSM (-9.4 [-12.1, -6.6]), but EAPC for Hispanics/Latino MSM was insignificant (-1.0 [-4.3, 2.4]). In comparison, HIV diagnoses in the unfunded THRIVE-eligible jurisdictions and the United States show White MSM experienced a decrease but to a lesser extent than THRIVE jurisdictions; Black MSM and Hispanic/Latino MSM did not see either a decline or an increase (Table). For most age groups, HIV diagnoses decreased in THRIVE jurisdictions among Black MSM, White MSM, and Hispanic/Latino MSM but increased in both unfunded THRIVE-eligible jurisdictions and the United States for Black MSM aged 25-34 years.

**Conclusion:** Findings suggest that successful implementation of HIV testing and PrEP in THRIVE contributed to decreases in HIV diagnoses among Black and White MSM. Barriers to HIV prevention for Hispanic/Latino MSM in THRIVE communities need to be understood to inform interventions for HIV prevention in this population.

Table. Estimated Annual Percent Change (EAPC) in HIV diagnoses among White, Black, and Hispanic/Latino MSM in U.S. Metropolitan Statistical Areas (MSAs) by total and stratified age groups and THRIVE funding, 2014-2018.

| Age group (years)        | MSA                           | EAPC (95% CI) in HIV diagnoses, 2014-2018 |                    |                     |
|--------------------------|-------------------------------|---|--------------------|---------------------|
|                          |                               | White MSM                                 | Black MSM          | Hispanic/Latino MSM |
| ≥13 (Total for all ages) | THRIVE funded                 | -9.4 (-12.1, -6.6)                        | -4.4 (-6.0, -2.7)  | -1.0 (-4.3, 2.4)    |
|                          | Not THRIVE funded             | -3.9 (-5.4, -2.3)                         | 0.5 (-0.8, 1.8)    | -0.9 (-2.0, 0.2)    |
|                          | United States and Puerto Rico | -4.2 (-4.9, -3.5)                         | -1.1 (-1.7, -0.5)  | 0.6 (-0.1, 1.3)     |
| 13-24                    | THRIVE funded                 | -9.6 (-16.7, -2.0)                        | -6.0 (-8.7, -3.3)  | -1.3 (-7.5, 5.3)    |
|                          | Not THRIVE funded             | -0.9 (-5.1, 3.5)                          | -2.8 (-4.9, -0.7)  | -4.0 (-6.3, -1.5)   |
|                          | United States and Puerto Rico | -1.6 (-3.5, 0.2)                          | -4.6 (-5.6, -3.6)  | -2.4 (-3.8, -1.0)   |
| 25-34                    | THRIVE funded                 | -4.5 (-9.3, 0.6)                          | -1.6 (-4.2, 1.1)   | -0.7 (-5.9, 4.7)    |
|                          | Not THRIVE funded             | -0.3 (-3.1, 2.7)                          | 3.9 (1.8, 6.0)     | 1.3 (-0.6, 3.2)     |
|                          | United States and Puerto Rico | -1.8 (-3.1, -0.5)                         | 2.7 (1.7, 3.8)     | 3.1 (2.0, 4.3)      |
| 35-44                    | THRIVE funded                 | -14.7 (-20.6, -8.3)                       | -4.1 (-8.6, 0.5)   | 0.1 (-7.2, 8.0)     |
|                          | Not THRIVE funded             | -6.9 (-10.3, -3.4)                        | 3.3 (-0.3, 7.1)    | -2.2 (-4.6, 0.3)    |
|                          | United States and Puerto Rico | -7.0 (-8.6, -5.4)                         | 0.3 (-1.4, 2.2)    | -1.3 (-2.9, 0.2)    |
| 45-54                    | THRIVE funded                 | -15.3 (-20.9, -9.3)                       | -9.7 (-15.3, -3.7) | -8.2 (-17.9, 2.7)   |
|                          | Not THRIVE funded             | -11.1 (-14.2, -7.8)                       | -5.6 (-9.7, -1.3)  | -0.8 (-3.9, 2.4)    |
|                          | United States and Puerto Rico | -9.7 (-11.2, -8.2)                        | -4.6 (-6.8, -2.5)  | -0.3 (-2.4, 1.7)    |
| >55                      | THRIVE funded                 | -4.6 (-12.6, 4.2)                         | -7.6 (-15.0, 0.4)  | 13.7 (-6.0, 37.6)   |
|                          | Not THRIVE funded             | 1.7 (-3.0, 6.5)                           | -1.5 (-7.6, 5.0)   | 1.5 (-3.7, 7.0)     |
|                          | United States and Puerto Rico | 0.3 (-1.8, 2.4)                           | -0.6 (-3.6, 2.6)   | 6.4 (2.7, 10.1)     |

**107 GENDER-AFFIRMING SURGERY ASSOCIATED WITH HIGH VIRAL SUPPRESSION AMONG TRANSGENDER PWH**

**Cristina Rodriguez-Hart<sup>1</sup>**, Gagarin Zhao<sup>1</sup>, Zil Goldstein<sup>2</sup>, Asa Radix<sup>2</sup>, Lucia Torian<sup>1</sup>

<sup>1</sup>New York City Department of Health and Mental Hygiene, Long Island City, NY, USA,

<sup>2</sup>Callen-Lorde Community Health Center, New York, NY, USA

**Background:**

Although HIV surveillance contains information on HIV outcomes among transgender people with HIV (TPWH), it does not include other important data, e.g., gender-affirming care, which may impact HIV outcomes such as viral suppression (VS). 79% of NYC TPWH are enrolled in Medicaid, and recent policy changes have extended coverage for gender-affirming healthcare. We matched Medicaid data with the NYC HIV Registry to ascertain the association of gender-affirming surgery and VS.

**Methods:**

Because Medicaid claims do not specify transgender status, an algorithm using sex, diagnosis codes, and prescriptions was developed and applied to Medicaid claims from 2013-2017. This cohort was matched to the HIV Registry to identify which TPWH obtained gender-affirming surgery. We compared VS among TPWH in Medicaid who had surgery to TPWH who did not access Medicaid and cisgender women and men. We compared VS by type of surgery and examined trends in VS pre- and post-surgery.

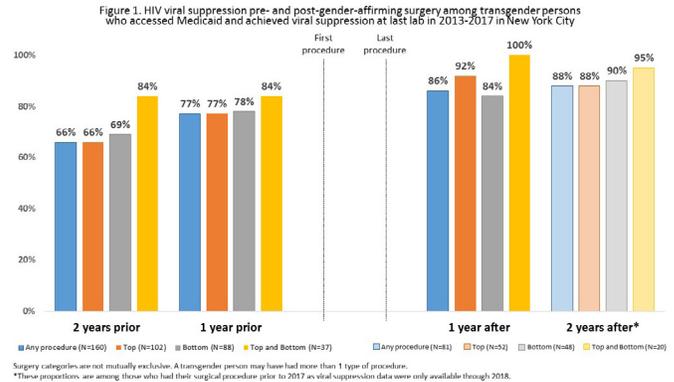
**Results:**

We identified 6,335 transgender persons in Medicaid in 2013-2017, 1,764 (28%) of whom were TPWH. 185 (10%) TPWH in Medicaid had gender-affirming surgery. They had higher VS at last lab and the greatest increase in VS over the five years (86.5%, 8.9% increase) compared to TPWH who did not access Medicaid (78.6%, 7.5% increase), cisgender women (82.3%, 8.7% increase), and cisgender men (84.1%, 6.9% increase). Those who had "bottom" surgery had the highest proportion suppressed (89%) compared to other types of surgery. VS increased pre-surgery, at least in part due to the common practice requiring viral suppression prior to surgery, and remained high over time (66.3% 2 years prior, 76.9% 1 year prior, 86.3% 1 year after (among everyone), and 87.7% 2 years after (among those who had surgery prior to 2017)).

**Conclusion:**

Medicaid is a valuable source of data on transgender individuals and can complement data collected by HIV surveillance. While we cannot determine causality, it appears that preparing for gender-affirming surgery may be an important motivator in becoming virally suppressed. Moreover, it is associated with sustained high viral suppression, which is known to lead to improved survival and quality of life. Expanding Medicaid programs to include gender-

**affirming surgical care may be associated with better health outcomes among TPWH.**



**108 HIV TRENDS AMONG THE AMERICAN INDIAN/ALASKA NATIVES, 2014-2018**

**Sophie Sembajwe<sup>1</sup>**, Andria Apostolou<sup>1</sup>, Jeffrey McCollum<sup>1</sup>, Azfar-E-Alam Siddiqi<sup>2</sup>, Irene Hall<sup>2</sup>, Jianmin Li<sup>2</sup>, Baohua Wu<sup>2</sup>

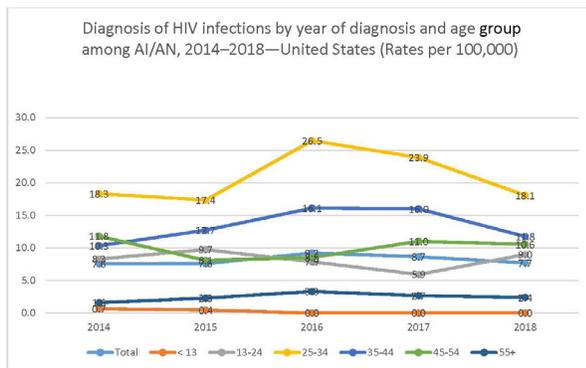
<sup>1</sup>Indian Health Service, Rockville, MD, USA, <sup>2</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** HIV diagnosis rates among American Indian/Alaska Natives (AI/AN) are higher than rates in whites and some minorities such as Asians. We evaluated HIV trends in diagnoses and mortality among AI/AN between 2014-2018.

**Methods:** We analyzed HIV surveillance data reported to CDC by state and local health departments focusing on the AI/AN population from 2014-2018. We focused on HIV diagnoses, prevalence of diagnosed cases and death rates per 100,000 AI/AN by age, sex, as well as Indian Health Service (IHS) geographic designations consisting of twelve physical areas of the United States: Alaska, Albuquerque, Bemidji, Billings, California, Great Plains, Nashville, Navajo, Oklahoma, Phoenix, Portland, and Tucson.

**Results:** Overall, from 2014 to 2018 the HIV diagnosis rate remained stable (2014: 7.6, 2018: 7.7 per 100,000). Increases were observed among those in the 13-24 years (8.2%) and 35-44 years (13.8%) age groups, with the latter having the highest percent increase among all age groups. Overall, the percentage of AI/AN living with diagnosed HIV increased 20.7% from 2014 to 2018. These increases were observed across almost all categories. Overall, the death rates from 2014-2018, decreased 31.4%. By IHS area, in 2018, the Navajo area experienced the highest HIV diagnosis rate per 100,000 population (13.9) followed closely by the Albuquerque (13.3) and Phoenix (12.7) areas. Nashville experienced the lowest HIV diagnosis rates during 2018 (1.8). In 2018, the majority of diagnoses across most IHS areas, were among men with HIV infection attributed to male-to-male sexual contact. In 2018, the Phoenix area had the highest rate per 100,000 of AI/AN persons living with HIV at 250.2, while Bemidji area had the lowest rate of AI/AN persons living with HIV at 44.0. In 2018, the Billings area experienced the highest death rates among AI/AN living with HIV, at 4.7 per 100,000 population. Bemidji, California, Nashville and Tucson areas reported no deaths in 2018.

**Conclusion:** The findings indicated that there have been increases in HIV diagnoses among AI/AN subgroups from 2014-2018, particularly in the 13-24 and 35-44 age groups. Furthermore, in 2018, the Navajo area experienced the largest burden of HIV diagnoses. In terms of HIV death rates, there have been general decreases across the board for AI/AN populations nationally and in IHS-area-specific jurisdictions.



## 109 LOWER UPTAKE OF DOLUTEGRAVIR AMONG WOMEN OF REPRODUCTIVE POTENTIAL VS MEN—KENYA

Matthew L. Romo<sup>1</sup>, Rena Patel<sup>2</sup>, Jessie Edwards<sup>3</sup>, John M. Humphrey<sup>4</sup>, Elizabeth A. Kelvin<sup>5</sup>, Mercy Maina<sup>6</sup>, Katarzyna Wyka<sup>5</sup>, Kara Wools-Kaloustian<sup>4</sup>, Denis Nash<sup>1</sup>, for IeDEA

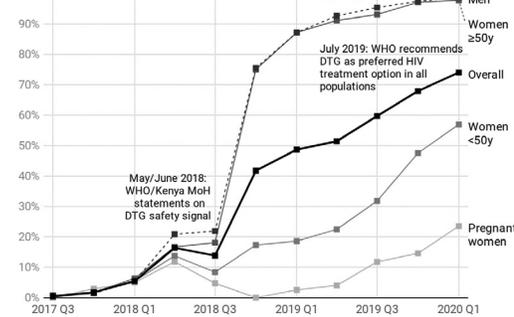
<sup>1</sup>City University of New York Institute for Implementation Science in Population Health, New York, NY, USA, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>4</sup>Indiana University, Indianapolis, IN, USA, <sup>5</sup>City University of New York, New York, NY, USA, <sup>6</sup>Moi Teaching and Referral Hospital, Eldoret, Kenya

**Background:** The transition to dolutegravir (DTG)-containing combination antiretroviral therapy (cART) is expected to benefit population health, but its use among women of reproductive potential—the largest group affected by the HIV epidemic in sub-Saharan Africa—has been controversial because of a potential association between DTG use at conception and neural tube defects. In July 2019, the World Health Organization (WHO) recommended DTG as the preferred treatment option for all populations with HIV. Given the changes in recommendations, we sought to examine potential disparities in DTG uptake. **Methods:** We used data from the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium for adults in Kenya at sites that had implemented DTG. We computed the proportion of individuals newly initiating cART with DTG and the cumulative proportion of individuals already on cART switching to DTG. We present these quarterly proportions overall and stratified by reproductive age and gender (women <50y, women ≥50y, men) and pregnancy status after site DTG implementation. We used hierarchical logistic regression to determine the association of reproductive potential and status with starting cART with DTG and switching to DTG-containing cART; models had a random intercept for site and were adjusted for receiving care before/after the July 2019 WHO recommendation.

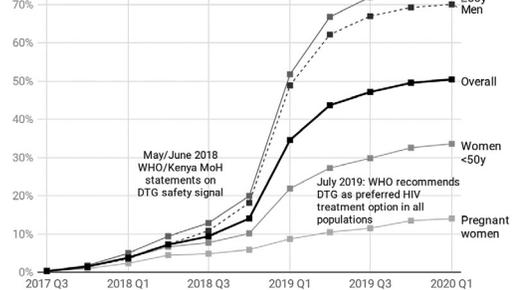
**Results:** Between July 2017–March 2020, 80,070 patients sought care, consisting of 48% women <50y, 14% women ≥50y, 34% men, and 5% pregnant women, and 20% of these patients started cART. Disparities in DTG uptake emerged in Q3 2018 (Figure). In Q1 2020, nearly all (≥98%) women ≥50y and men were starting cART with DTG compared with 57% of women <50y and 24% of pregnant women; about three-quarters (>70%) of treatment-experienced women ≥50y and men had switched to DTG-containing cART compared with 34% of women <50y and 14% of pregnant women. During follow-up, women <50y and pregnant women had significantly lower odds of starting cART with DTG (adjusted odds ratio [aOR] 0.18 and 0.04, respectively; both  $p < 0.001$ ), and switching to DTG (aOR 0.15 and 0.04, respectively; both  $p < 0.001$ ), compared with men.

**Conclusion:** We identified major disparities in DTG uptake among women of reproductive potential and pregnant women in Kenya. Efforts should focus on equitable access to DTG and increasing its uptake among women of reproductive potential who are starting or already on cART.

## Quarterly proportion of treatment-naïve individuals starting cART with a DTG-containing regimen



## Cumulative proportion of treatment-experienced individuals switching to DTG-containing cART



Created with Datawrapper

## 110 RCT OF AN ONLINE MENTAL HEALTH INTERVENTION AMONG OLDER PLWH DURING COVID-19 PANDEMIC

Jeff Berko<sup>1</sup>, Peter Mazonson<sup>1</sup>, Duncan Short<sup>2</sup>, Cassidy Gutner<sup>3</sup>, Maile Karris<sup>4</sup>, Gregory Huhn<sup>5</sup>, Lynsay MacLaren Ehui<sup>6</sup>, Theoren Loo<sup>1</sup>, Sarah-Marie Chan<sup>1</sup>, Frank Spinelli<sup>3</sup>, Andrew Zolopa<sup>3</sup>

<sup>1</sup>Mazonson and Santas, Inc., Larkspur, CA, <sup>2</sup>Viv Healthcare, London, UK, <sup>3</sup>Viv Healthcare, Research Triangle Park, NC, USA, <sup>4</sup>University of California San Diego, San Diego, CA, USA, <sup>5</sup>Ruth M Rothstein CORE Center, Chicago, IL, USA, <sup>6</sup>Whitman-Walker Health, Washington, DC, USA

**Background:** Older adults (≥50 y) living with HIV (OALWH) may experience elevated levels of depression, anxiety, and loneliness. Online mindfulness lessons have the potential to ameliorate these problems and enhance access, especially during the COVID-19 pandemic. The objective of this randomized controlled trial was to determine the effectiveness of online mindfulness lessons in reducing feelings of depression, anxiety, and loneliness among OALWH.

**Methods:** The study was conducted between May and August 2020. Individuals with any degree of self-reported loneliness at baseline were eligible to participate. Outcomes of interest included depression, measured using the Center for Epidemiologic Studies Depression Scale (CES-D-10), anxiety measured using the Generalized Anxiety Disorder (GAD-7), and loneliness measured using both the Three-item Loneliness Scale (3IL) and a Daily Diary that asked "How lonely do you feel today?" Two sample t-tests were used to compare group scores at follow-up.

**Results:** Of 214 participants who were randomized, the mean (SD) age was 60.4 (5.9) years, 89% were male, 69% were white, and 74% were gay or lesbian. At the end of the 25-day intervention, the intervention group demonstrated reduced levels of depression (2.6 point improvement;  $p < 0.01$ ), and reduced levels of anxiety (1.5 point improvement;  $p = 0.03$ ) compared to the control group (Table 1). Among the subset of participants with elevated baseline depression scores (defined as CES-D-10 ≥ 8), the between-group improvement in depression scores was greater (4.2 point improvement;  $p < 0.01$ ). Similarly, among the subset of participants with elevated baseline anxiety scores (defined as GAD-7 ≥ 5), the between-group improvement in anxiety scores was greater (2.4 point improvement;  $p < 0.01$ ). Loneliness improved significantly, as indicated by the Daily Diary, for those with at least moderate loneliness at baseline (0.7 point improvement;  $p < 0.01$ ).

**Conclusion:** This randomized controlled trial is the first to show that a series of brief, online mindfulness audio lessons improves mental health outcomes

among OALWH who report some degree of loneliness. For many patients, this intervention may offer emotional relief, particularly with regard to depression and anxiety, even in the face of the COVID-19 pandemic.

**Table 1. Mean depression, anxiety and loneliness scores following an online mindfulness intervention**

|                                | Intervention Mean (SD) | Control Mean (SD) | p-value | Difference | Cohen's d |
|--------------------------------|------------------------|-------------------|---------|------------|-----------|
| <b>Depression<sup>a</sup></b>  |                        |                   |         |            |           |
| All participants               | 10.2 (5.8)             | 12.8 (6.9)        | < 0.01  | 20.3%      | 0.41      |
| Depressed at baseline (CESD≥8) | 11.8 (5.6)             | 16.0 (5.8)        | < 0.01  | 26.3%      | 0.75      |
| <b>Anxiety<sup>b</sup></b>     |                        |                   |         |            |           |
| All participants               | 5.2 (4.3)              | 6.7 (5.0)         | 0.03    | 22.4%      | 0.32      |
| Anxious at baseline (GAD≥5)    | 6.2 (4.2)              | 8.6 (4.5)         | < 0.01  | 25.9%      | 0.55      |
| <b>Loneliness<sup>c</sup></b>  |                        |                   |         |            |           |
| All participants (3IL)         | 6.0 (1.9)              | 6.3 (1.8)         | 0.26    | 4.7%       | 0.16      |
| Lonely at baseline (3IL≥6)     | 6.8 (1.6)              | 7.3 (1.5)         | 0.06    | 6.8%       | 0.33      |
| All participants (Diary)       | 2.7 (1.5)              | 3.1 (1.6)         | 0.07    | 12.9%      | 0.26      |
| Lonely at baseline (Diary)     | 3.0 (1.4)              | 3.7 (1.5)         | < 0.01  | 18.9%      | 0.55      |

<sup>a</sup> Measured using the CES-D-10, which ranges from 0-30 with higher scores indicating more severe depression.  
<sup>b</sup> Measured using the GAD-7, which ranges from 1-21, with higher scores indicating more severe anxiety.  
<sup>c</sup> Measured using the Three-Item Loneliness scale, which ranges from 3-9, with higher scores indicating more loneliness, and using a Daily Diary, which asked "How lonely did you feel today?" on a 1-7 scale, with higher scores indicating more loneliness, each day for three days. Responses were averaged across the three days.

**111 FEE FOR HOME DELIVERY AND MONITORING OF ART RAISES VIRAL SUPPRESSION IN SOUTH AFRICA**

**Ruanne Barnabas<sup>1</sup>, Adam Szpiro<sup>1</sup>, Xolani Ntinga<sup>2</sup>, Melissa Mugambi<sup>1</sup>, Meighan Krows<sup>1</sup>, Torin Schaafsma<sup>1</sup>, Theodore Zhao<sup>1</sup>, Heidi Van Rooyen<sup>2</sup>, Jared Baeten<sup>1</sup>, Connie L. Celum<sup>1</sup>, Andrew Bruce<sup>1</sup>, Alastair Van Heerden<sup>2</sup>, for the Deliver Health Study Team**  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Human Sciences Research Council, Pretoria, South Africa

**Background:**

Home delivery and monitoring of antiretroviral therapy (ART) is convenient, overcomes logistic barriers, and could increase ART adherence and viral suppression particularly among men who engage less in clinic-based HIV care than women. If clients pay for this service and the benefits are sufficient, it could be a scalable strategy.

**Methods:**

We conducted a randomized trial, the Deliver Health Study, of a fee for home delivery and monitoring of ART compared to clinic ART delivery in Pietermaritzburg, KwaZulu Natal, South Africa. People living with HIV on ART or willing to initiate ART in the community were recruited through community-based testing or from facilities and randomized to: 1) fee for home delivery and monitoring of ART; or 2) clinic-based ART (standard of care). The one-time fee for home delivery was tiered based on participant income (ZAR 30, 60, and 90; equivalent to \$2, 4, 6). The outcomes were payment of the fee for home delivery; acceptability of the delivery service; and viral suppression, assessed using log-linear regression adjusting for gender and age.

**Results:**

From October 2019-January 2020, 400 persons were screened; of the 180 persons living with HIV, 162 were enrolled - 82 randomized to the fee for home delivery group and 80 to the standard of care group. Overall, 87 participants (54%) were men, 22% were <30 years, 101 (62%) were on ART, and 98 (60%) were unemployed. Among participants in the fee for home delivery group, 40 (49%), 32 (40%), and 9 (11%) were in the ZAR 30, 60, and 90 fee groups, respectively. Median follow-up was 47 weeks (IQR 43-50 weeks) spanning COVID-19 restrictions. Retention at exit was 96%. In the fee payment group, 98% of participants paid the full user fee and acceptability was high with 100% reporting willingness to continue to pay a fee. Compared to standard clinic care, in the intent-to-treat analysis, fee for home delivery of ART significantly increased viral suppression from 74% to 88% (RR=1.21, 95% CI: 1.02-1.42) with a RR of 1.31 among men; fee group (84%, RR=1.31, 95% CI: 1.01-1.71) compared to standard of care (64%).

**Conclusion:**

Among South African adults living with HIV on ART or initiating ART, a fee for home delivery and monitoring of ART significantly increased viral suppression compared to clinic-based ART. Client payment of a fee for home delivery and monitoring of ART was highly acceptable in the context of low income and high unemployment, and improved health outcomes as a result.

**112 IFITM PROTEINS PROMOTE SARS-CoV-2 INFECTION IN HUMAN LUNG CELLS**

**Caterina Prelli Bozzo<sup>1</sup>, Rayhane Nchioua<sup>1</sup>, Meta Volcic<sup>1</sup>, Daniel Sauter<sup>1</sup>, Jan Muench<sup>1</sup>, Konstantin Sparrer<sup>1</sup>, Frank Kirchhoff<sup>1</sup>**  
<sup>1</sup>Ulm University Medical Center, Ulm, Germany

**Background:**

Interferon-induced transmembrane proteins (IFITMs 1, 2 and 3) are a family of interferon (IFN) stimulated genes (ISGs) well-known to inhibit entry of numerous enveloped viruses including the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). However, the mechanism(s) underlying the antiviral activity of IFITM proteins are not fully understood and most evidence comes from single-round pseudoparticle infection assays of cells artificially overexpressing IFITM proteins. Here, we examined whether and how endogenous IFITM proteins may affect infection by the novel pandemic coronavirus SARS-CoV-2.

**Methods:**

SARS-CoV-2 Spike (S) and ACE2 mediated pseudoparticle entry in HEK293T cells overexpressing IFITMs was quantified using luciferase reporter assays. To determine the role of IFITMs under more physiological conditions, we silenced IFITM protein expression in Calu-3 cells and in primary airway epithelial cells (SAEC) using siRNAs and infected them with genuine SARS-CoV-2. Viral entry and replication were quantified by qRT-PCR as well as plaque assays. To clarify whether IFITMs represent suitable therapeutic targets, we analyzed whether antibodies against IFITM proteins inhibit SARS-CoV-2 infection of lung cells.

**Results:**

Our results show that overexpression of IFITM protein blocks ACE2 and SARS-CoV-2 Spike mediated pseudoparticle infection. In striking contrast, however, endogenous IFITM expression was required for efficient entry and replication of genuine SARS-CoV-2 in Calu-3 lung cells and primary lung cells both in the presence and absence of interferons. Efficient endogenous expression of IFITM1 and IFITM2 enhanced SARS-CoV-2 replication in Calu-3 and SAEC by several orders of magnitude. In addition, antibodies directed against IFITM proteins inhibited SARS-CoV-2 replication in lung cells.

**Conclusion:**

IFITM proteins are cofactors for efficient SARS-CoV-2 infection of human lung cells and represent novel, unexpected targets for the treatment of COVID-19.

**113 SARBECoVIRUS ORF6 PROTEINS ANTAGONIZE INTERFERON SIGNALING**

**Izumi Kimura<sup>1</sup>, Keiya Uriu<sup>1</sup>, Yoriyuki Konno<sup>1</sup>, Daniel Sauter<sup>2</sup>, So Nakagawa<sup>3</sup>, Kei Sato<sup>1</sup>**, for Institute of Molecular Virology, Ulm University Medical Center, Germany  
<sup>1</sup>University of Tokyo, Tokyo, Japan, <sup>2</sup>Ulm University Medical Center, Ulm, Germany, <sup>3</sup>Tokai University School of Medicine, Kanagawa, Japan

**Background:** SARS-CoV and SARS-CoV-2 are closely related, both belong to the genus Betacoronavirus, subgenus Sarbecovirus. The ORF6 gene is commonly encoded in all Sarbecoviruses, including SARS-CoV and SARS-CoV-2, while no orthologs are found in the other Betacoronaviruses. A comprehensive proteome analysis by Gordon et al. has recently suggested that SARS-CoV-2 ORF6 interacts with two cellular proteins, RAE1 and NUP98, via its C-terminal region, but the biological function of ORF6 remains unknown.

**Methods:** For the cell culture experiments, we generated a series of Sarbecovirus ORF6 expression plasmids. We monitored human IFNβ1 promoter activity in the presence of ORF6 by a luciferase reporter assay. To determine the residue(s) that are responsible for the anti-interferon (IFN) activity of ORF6, we aligned and compared the ORF6 amino acid sequences and prepared a series of ORF6 mutants. To verify whether ORF6 interacts with RAE1 and NUP98 proteins, we performed co-immunoprecipitation assay.

**Results:** The cell culture experiments showed that ORF6 inhibits the induction of type I IFN upon viral infection. Intriguingly, the anti-IFN activity of ORF6 proteins of SARS-CoV-2 lineages was more potent than that of SARS-CoV lineages. Mutational analyses identified the two residues in the C-terminal region of ORF6 that determines the difference on the anti-IFN activity between SARS-CoV-2 ORF6 and SARS-CoV ORF6. Moreover, the co-immunoprecipitation assay revealed that ORF6 binds to RAE1 and NUP98 via its C-terminus, thereby inhibiting the expression of IFNβ1 mRNA. Finally, in approximately 0.2% of the SARS-CoV-2 isolates during current pandemic, we identified naturally occurring variants that encode the truncated ORF6 gene by frameshift mutation and potentially result in the incompetence of exhibiting anti-IFN effect.

**Conclusion:** Our findings suggest that the poor IFN activation observed in COVID-19 patients can at least in part be ascribed to ORF6. Furthermore, we

provide evidence suggesting that the emergence of the SARS-CoV-2 variants that lost a functional ORF6 gene may contribute to the attenuation of viral pathogenicity.

## 114 SEVERE COVID-19 IS FUELED BY DISRUPTED GUT BARRIER INTEGRITY

Leila B. Giron<sup>1</sup>, Harsh Dweep<sup>1</sup>, Xiangfan Yin<sup>1</sup>, Han Wang<sup>1</sup>, Mohammad Damra<sup>1</sup>, Aaron R. Goldman<sup>1</sup>, Clovis S. Palmer<sup>2</sup>, Hsin-Yao Tang<sup>1</sup>, Maliha W. Shaikh<sup>3</sup>, Netanel F. Zilberstein<sup>3</sup>, Qin Liu<sup>1</sup>, Andrew Kossenkov<sup>1</sup>, Ali Keshavarzian<sup>3</sup>, Alan Landay<sup>3</sup>, Mohamed Abdel-Mohsen<sup>1</sup>

<sup>1</sup>Wistar Institute, Philadelphia, PA, USA, <sup>2</sup>Burnet Institute, Melbourne, Australia, <sup>3</sup>Rush University Medical Center, Chicago, IL, USA

### Background:

A disruption of the crosstalk between gut and lung has been implicated as a driver of severity during several respiratory-related diseases. Lung injury causes systemic inflammation, which disrupts gut barrier integrity, increasing the permeability to gut microbes and their products. This exacerbates inflammation, resulting in positive feedback. We applied a multi-omic systems biology approach to investigate the potential link between loss of gut barrier integrity and Coronavirus disease 2019 (COVID-19) severity.

### Methods:

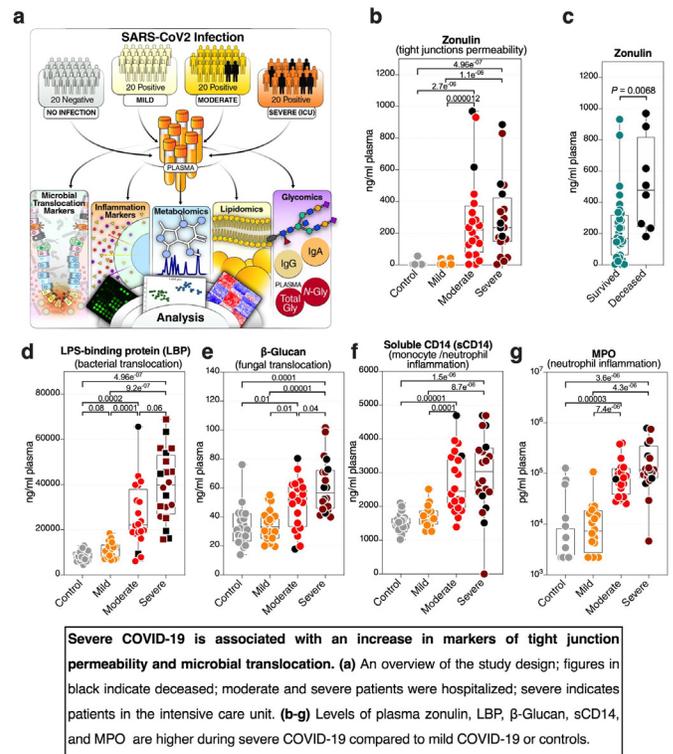
We analyzed plasma samples from age and gender-matched COVID-19 patients (n=60) with varying disease severity (mild, moderate, and severe) and 20 SARS-CoV-2 negative controls. We measured markers and drivers of tight junction permeability and microbial translocation using ELISA; inflammation and immune activation markers using ELISA and multiplex cytokine arrays; untargeted metabolomic and lipidomic analyses using mass spectrometry; and plasma glycomes using capillary electrophoresis and lectin microarray. False discovery rate (FDR) was calculated to account for multiple comparisons.

### Results:

Our data indicate, first, that severe COVID-19 is associated with a dramatic increase in the level of zonulin (FDR<0.00001), the only known physiological driver of intestinal tight junction permeability. This increased permeability associated with translocation of both bacterial (LPS binding protein (LBP) levels) and fungal ( $\beta$ -glucan levels) products into blood (FDR<0.01). The degree of intestinal permeability and microbial translocation strongly correlated with increased systemic inflammation (correlations with IL-6 and other inflammatory cytokines and markers) (FDR>0.05). Second, levels of metabolomic and lipidomic markers of gut and gut microbiota functionality including citrulline (a marker of healthy gut; decreased), succinic acid, and tryptophan catabolism metabolites (markers of microbial dysbiosis; increased) were disrupted during severe COVID-19 (FDR<0.05). Finally, the gut microbiome is known to release enzymes that degrade plasma glycans, which regulate inflammation and complement activation. Indeed, severe COVID-19 was associated with loss of the anti-complement activation galactosylated glycans from plasma and IgG glycoproteins (FDR<0.05).

### Conclusion:

Our data provide multiple layers of evidence that a previously unappreciated factor with significant clinical implications, disruption in gut barrier integrity, is a potential force that contributes to COVID-19 severity.



## 115 SARS-CoV-2 PERSISTS IN INTESTINAL ENTEROCYTES UP TO 7 MONTHS AFTER SYMPTOM RESOLUTION

Minami Tokuyama<sup>1</sup>, Mark S. Ladinsky<sup>2</sup>, Divya Jha<sup>1</sup>, Francesca Cossarini<sup>1</sup>, Alexandra E. Livanos<sup>1</sup>, Jason Reidy<sup>1</sup>, Michael Tankelevich<sup>1</sup>, Gustavo Martinez-Delgado<sup>1</sup>, Pamela J. Bjorkman<sup>2</sup>, Saurabh Mehandru<sup>1</sup>

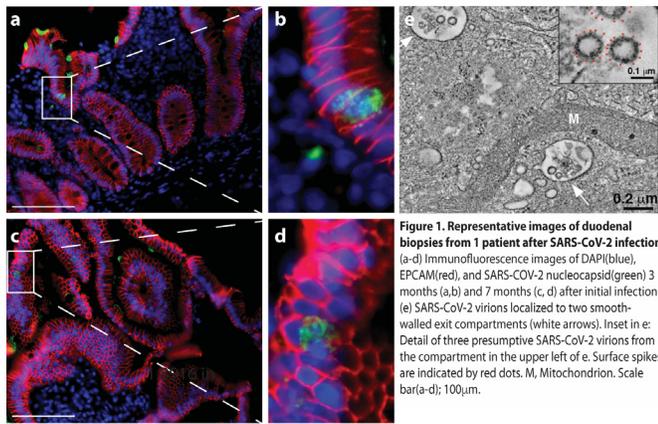
<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>2</sup>California Institute of Technology, Pasadena, CA, USA

**Background:** Host proteins ACE-2 and TMPRSS2 facilitate SARS-CoV-2 infection and are expressed in the lungs as well as the intestinal tract, particularly in the small bowel. Gastrointestinal symptoms represent the most common extrapulmonary manifestation of COVID-19. Viral RNA has been isolated from fecal samples from COVID-19 patients, where it can persist longer than detection in nasopharyngeal swabs. While SARS-CoV-2 infection of enterocytes has been demonstrated in vitro, in vivo studies are lacking.

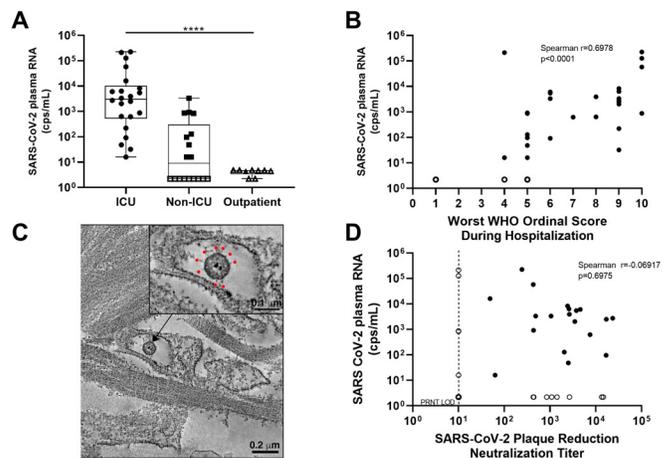
**Methods:** Small intestinal biopsies from patients who underwent clinically indicated endoscopic procedures after a positive SARS-CoV-2 nasopharyngeal swab (n=27) or were found to have positive serology (n=2) were analyzed by immunofluorescence (IF) (n=25) and electron microscopy (EM) (n=14) for the presence of virus. Clinical details were also collected.

**Results:** Sixteen of 29 patients had detectable SARS-CoV-2 antigen by either IF or EM (Figure 1). Virus was restricted to the epithelium and patchy in distribution. Virus was detected as soon as 15 days after symptom onset and persisted up to 6 months after symptom resolution. Five patients were nasopharyngeal swab positive at the time of procedure and, of these, 4 had detectable antigen on biopsy. Despite the presence of virus, only 9/16 patients had any signs of inflammation on histology, and when present, this was mild. In two patients where virus was present at 3 months and 4 months, additional biopsies were obtained at 7 months and 6 months, respectively. Viral antigen was persistently detected in both patients and both patients were nasopharyngeal swab negative for all procedures. Interestingly, only 37.5% (6 of 16) of patients with virus detected in the small bowel had GI symptoms (diarrhea, nausea or vomiting) during their acute COVID-19 illness as compared to 46.1% (6/13) of patients where no virus could be detected in the intestines.

**Conclusion:** SARS-CoV-2 infects enterocytes in humans in vivo and can persist in the intestines up to 7 months following symptoms resolution. This persistence is not associated with an overt inflammatory infiltrate and does not appear to correlate with presence of GI symptoms in the acute COVID-19 setting.



**Figure 1.** Representative images of duodenal biopsies from 1 patient after SARS-CoV-2 infection (a-d) immunofluorescence images of DAPI (blue), EPCAM (red), and SARS-CoV-2 nucleocapsid (green) 3 months (a, b) and 7 months (c, d) after initial infection. (e) SARS-CoV-2 virions localized to two smooth-walled exit compartments (white arrows). Inset in e: Detail of three presumptive SARS-CoV-2 virions from the compartment in the upper left of e. Surface spikes are indicated by red dots. M, Mitochondrion. Scale bar (a-d): 100µm.



**116 COVID-19 OUTCOME: INSIGHTS FROM QUANTIFICATION OF VIREMIA AND NEUTRALIZING ANTIBODY**

**Jana L. Jacobs<sup>1</sup>**, Brittany Staines<sup>1</sup>, William Bain<sup>1</sup>, Priscila Da Silva Castanha<sup>1</sup>, Asma Naqvi<sup>1</sup>, Valerie F. Boltz<sup>2</sup>, Ernesto T. Marques<sup>1</sup>, Thomas Denny<sup>3</sup>, Christopher Woods<sup>3</sup>, Alison Morris<sup>1</sup>, Mary F. Kearney<sup>4</sup>, Mark S. Ladinsky<sup>5</sup>, Pamela J. Bjorkman<sup>5</sup>, Georgios D. Kitsios<sup>1</sup>, John W. Mellors<sup>1</sup>  
<sup>1</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>2</sup>National Institutes of Health, Frederick, MD, USA, <sup>3</sup>Duke University School of Medicine, Durham, NC, USA, <sup>4</sup>National Cancer Institute, Frederick, MD, USA, <sup>5</sup>California Institute of Technology, Pasadena, CA, USA

**Background:** Although SARS-CoV-2 "RNAemia" (viral RNA in blood) has been detected in patients with COVID-19, more often in severe disease, important questions remain: 1) Is the viral RNA in blood in cell-free virions? 2) Is the level of viremia prognostic? 3) Are viremia and neutralizing antibody titer related? We investigated these questions using multiple complementary approaches.

**Methods:** We developed an internally-controlled, ultrasensitive (1 copy/ extraction) qRT-PCR assay for SARS-CoV-2 N gene RNA and applied this assay to plasma samples (0.5 – 1.0 ml) from COVID-19 outpatients and inpatients with variable severity of illness by WHO scale. For a subset of samples, we centrifuged plasma at 21,000xg for 2 hours, assayed viral RNA in both pelleted and supernatant fractions, and performed electron tomography on the pelleted fraction. SARS-CoV-2-specific antibody titers were determined using S1 and N EIAs and neutralizing antibody titers by infectious virus plaque reduction assay.

**Results:** SARS-CoV-2 RNA was detected in plasma of 22/22 (100%) ICU patients, 9/18 (50%) non-ICU patients and 1/9 outpatients. Plasma viral RNA levels were significantly higher in ICU > non-ICU > outpatients (Fig 1A;  $p < 0.0001$  by Kruskal Wallis test), and among inpatients were strongly correlated with WHO score at admission (Spearman  $r = 0.5338$ ,  $p = 0.0006$ ), maximum WHO score during hospitalization (Fig 1B; Spearman  $r = 0.6978$ ,  $p < 0.0001$ ) and clinical outcomes of death, discharge to hospital-level care, discharge to home or discharge asymptomatic ( $p = 0.0035$  by Kruskal Wallis test). 80% of viral RNA was recovered in the pelleted fraction after centrifugation, and characteristic virions were observed in the pelleted fraction by electron tomography (Fig 1C). Neutralizing antibody titers showed no overall correlation with plasma viral RNA (Fig 1D) but revealed distinct subgroups with higher level viremia (>1000 copies/ml) and either low titer (<100) or higher titer (>100) neutralizing antibody.

**Conclusion:** SARS-CoV-2 viremia quantified by ultrasensitive RT-PCR was detected in 100% of ICU patients and 50% of non-ICU inpatients. The level of viremia correlated with disease severity and outcome, which may prove useful for clinical decision making. A subgroup of hospitalized patients with high-level viremia and low neutralizing antibody may be the best candidates for antibody therapy.

**117 CHARACTERIZATION AND EPIOTOPE MAPPING OF SARS-CoV-2-SPECIFIC T CELLS**

**Kristin L. Boswell<sup>1</sup>**, Phillip A. Swanson<sup>1</sup>, Giune Padilla<sup>1</sup>, Adrian McDermott<sup>1</sup>, Martin R. Gaudinski<sup>1</sup>, Richard A. Koup<sup>1</sup>  
<sup>1</sup>National Institutes of Health, Bethesda, MD, USA

**Background:** The role that CD4+ and CD8+ T cells play in the protection from and disease severity of COVID-19 is not completely understood. A better understanding of T cell function and the epitopes that they target will be invaluable in the development of the next generation of vaccines and therapeutics. To better understand the role of T cells, we characterized the frequency, effector functions and phenotype of SARS-CoV-2-specific CD4+ and CD8+ T cells in a cohort of patients who recovered from COVID-19, and identified multiple peptides that contain T cell epitopes within the Spike protein (S), Nucleocapsid protein (N) and Membrane protein (M).

**Methods:** The frequency and phenotype of SARS-CoV-2-specific T cells from convalescent patients with mild or moderate disease (n=27, 25 to 92 days post-symptom onset) were determined by polychromatic flow cytometry and intracellular cytokine staining (ICS). Cells were stimulated for 6 hours with peptide pools corresponding to S, N and M. Cytokine production, memory phenotype, chemokine receptor expression and PD-1 expression were analyzed. For a subset of individuals (n = 19 for S; n=14 for N and M), IFNγ ELISpot assays and peptide matrices were utilized to identify peptides that contain T cell epitopes.

**Results:** CD4+ T cell responses to S, N and/or M were detected in almost all donors by ICS and were predominantly a Th1-type response as determined by cytokine production (IFNγ, IL-2 or TNF) and expression of CXCR3. A majority of the antigen-specific CD4+ cells were found in the effector memory compartment. Although less robust than the CD4+ T cell response, antigen-specific CD8+ T cells were detected in a majority of donors, were found within the effector memory compartments and displayed modest PD-1 upregulation. Multiple peptides that contain T cell epitopes were identified by IFNγ ELISpot (Figure 1). Some of the most commonly identified peptides include S42 (amino acids 165-179; 7/19 donors), S205 (a.a. 817-831; 10/19 donors), N83 (a.a. 329-343; 7/14 donors), M37 (a.a. 145-159; 8/14 donors) and M45 (a.a. 177-191; 10/14 donors).

**Conclusion:** These data suggest that T cells that target S, N and M play an important role in the immune response to SARS-CoV-2 and should be considered in future vaccine development. Further studies such as transcriptomic analysis and the TCR usage in longitudinal samples will provide a better understanding of epitope-specific T cells and their longevity.

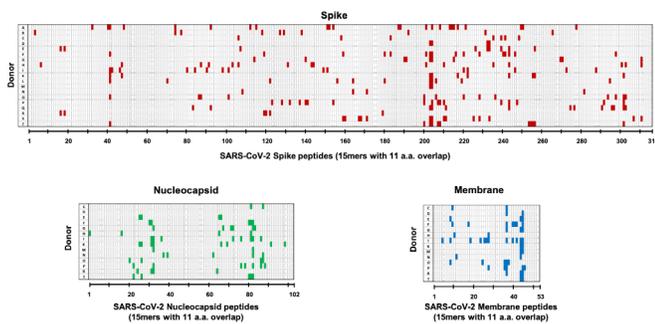


Figure 1. Peptides that elicited a positive response by IFNg ELISpot

## 118 BARICITINIB LOWERS INFLAMMATION AND PATHOLOGY IN SARS-CoV-2-INFECTED RHESUS MACAQUES

**Timothy Hoang**<sup>1</sup>, Maria Pino<sup>1</sup>, Arun Boddapati<sup>1</sup>, Elise Viox<sup>1</sup>, Carly E. Starke<sup>2</sup>, Amit Upadhyay<sup>1</sup>, Sanjeev Gumber<sup>1</sup>, Susan Pereira Ribeiro<sup>1</sup>, Rafick-Pierre Sékaly<sup>1</sup>, Rebecca Levit<sup>1</sup>, Jacob Estes<sup>2</sup>, Thomas H. Vanderford<sup>1</sup>, Raymond Schinazi<sup>1</sup>, Steven Bosinger<sup>1</sup>, Mirko Paiardini<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Oregon Health and Sciences University, Portland, OR, USA

**Background:** The emergence of SARS-CoV-2 and COVID-19 pandemic has placed an excessive burden on public and private healthcare systems with over 1,400,000 deaths worldwide. Thus, therapeutics aimed at mitigating disease severity are urgently needed. Immunological features of COVID-19 progression include an influx of innate and adaptive immune cells to the lung, with severe cases having elevated levels of pro-inflammatory cytokines and chemokines. Baricitinib is an oral, selective inhibitor of JAK 1/2 with potent anti-inflammatory activity approved for patients with moderate to severe active rheumatoid arthritis and predicted to have anti-SARS-CoV-2 effects based on in silico modeling.

**Methods:** 8 rhesus macaques (RMs) were infected with  $1.1 \times 10^6$  PFU SARS-CoV-2; at 2 days post infection (dpi), 4 of the 8 RMs began daily baricitinib treatment (4 mg/day). Nasal and throat swabs were collected daily for viral load; longitudinal blood and bronchoalveolar lavage (BAL) samples were collected for viral load, flow cytometry, cytokines and RNAseq analysis and at 10/11 dpi all RMs were euthanized for pathological analyses.

**Results:** Baricitinib was found in plasma and in the lungs of all treated RMs and was safe and well tolerated. Viral replication dynamics measured from nasal and throat swabs, BAL and lung at necropsy were not reduced with baricitinib. Innate Type-I IFN antiviral responses and adaptive SARS-CoV-2-specific T-cell responses remained similar between the two groups. RMs treated with baricitinib showed reduced inflammation (ferritin, CRP, histology), T cell immune activation and proliferation, neutrophil NETosis activity, and lung pathology, with decreased type 2 pneumocyte hyperplasia, peribronchiolar hyperplasia, and inflammatory cell infiltration. Importantly, baricitinib treated RMs had a rapid and remarkably potent suppression of alveolar macrophage production of cytokines (IL-6, TNF $\alpha$ , IL-10, IL-1 $\beta$  and IFN $\beta$ ) and chemokines (CCL4L1, CXCL10, CXCL3 and CXCL8) responsible for a pro-inflammatory environment and for the recruitment of neutrophil and pro-inflammatory monocytes. Additionally, we identified that a population of MARCO-macrophages are the primary producers of pro-inflammatory cytokines and are reduced in the lungs of baricitinib treated animals.

**Conclusion:** These data provide rationale and mechanistic insight for the use of baricitinib as a frontline therapeutic to reduce systemic inflammation induced following SARS-CoV-2 infection.

## 119 ONE DOSE OF COVID-19 mRNA VACCINE IN SARS-CoV-2-EXPERIENCED PEOPLE MAY BE SUFFICIENT

**Marie I. Samanovic-Golden**<sup>1</sup>, Amber M. Cornelius<sup>1</sup>, Trishala Karmacharya<sup>1</sup>, Jimmy Wilson<sup>1</sup>, Sophie L. Gray-Gaillard<sup>1</sup>, Joseph M. Allen<sup>1</sup>, Sara W. Hyman<sup>1</sup>, Ramin S. Herati<sup>1</sup>, Mark Mulligan<sup>2</sup>, for NYU Infectious Diseases with Public Health Importance (IDPHI) Study Team

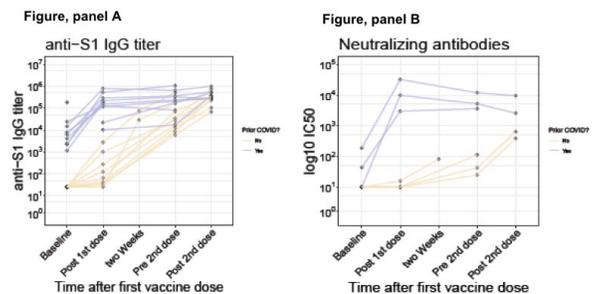
<sup>1</sup>New York University Langone Medical Center, New York, NY, USA, <sup>2</sup>New York University, New York, NY, USA

**Background:** Understanding if single doses of SARS-CoV-2 mRNA vaccines in SARS-CoV-2-experienced people are fully protective is a public health priority. This study measured immune responses before and after mRNA vaccine in people with or without histories of COVID-19.

**Methods:** Specimens were collected from participants before and 6-14 days after doses 1 and 2. Humoral assays included an S1-specific Ig ELISA and a live-virus microneutralization assay (MN) vs the original SARS-CoV-2 USA-WA1/2020 strain. ELISpot assays and 36-color spectral analysis flow cytometry assessed B- and T-cell responses.

**Results:** 32 adults received Pfizer BioNTech vaccine and 1 received Moderna vaccine. 14 had a history of COVID-19 (median age 41, 71% female, 10 with 3/20 and 2 with 12/20 illness onset, 2 asymptomatic). 19 were SARS-CoV-2-naïve (median age 39, 47% female). S1-specific IgG/A/M ASC were detected readily by ELISpot 6-14 days after dose 1 and were higher in SARS-CoV-2-experienced (median: 200) than -naïve (median: 27) subjects; after dose 2, the converse was observed (medians 53 vs 293). By flow cytometry, T cell activation was broadly observed 6-14 days after 1st vaccination, with increases in CD4+ or CD8+ T cells expressing CD38 and Ki67 (CD4: median fold-changes 1.6 for SARS-CoV-2-experienced and 1.8 for -naïve; CD8: 3.1 and 2.2). S1-specific IgG was present at baseline in experienced subjects (median: 6320), peaked at 6-14 days post-dose 1 (median: 169000), and wasn't boosted by dose 2 (panel A). In naïve participants, S1-specific IgG was not present at baseline, low at day 6-14 (median: 66), higher at day 21 (median: 27000), and boosted by dose 2 (median: 188000). Interestingly, by 6-14 days after dose 2, experienced and naïve subjects had similar S1-specific IgG titers. The MN titers followed a similar pattern (panel B): in experienced subjects, striking increases after dose 1 (median: 9860) but no boosting by dose 2; in naïve subjects, no neutralization was observed at 6-14 days, low titers were present at 21 days post-dose 1 (median: 43), with boosting after dose 2 (median: 513).

**Conclusion:** People with a history of SARS-CoV-2 infection who received a single dose of mRNA vaccine produced binding and neutralizing antibody titers at 6-14 days that were similar to, or higher than, titers in SARS-CoV-2-naïve people who had received 2 doses. Their titers were not boosted by a second dose. These findings support a hypothesis that SARS-CoV-2-experienced people may require only a single dose of mRNA vaccine.



## 120 SARS-CoV-2 RECRUITS A HAEM METABOLITE TO EVADE ANTIBODY IMMUNITY

**Annachiara Rosa**<sup>1</sup>, Valerie E. Pye<sup>1</sup>, Carl Graham<sup>1</sup>, Luke Muir<sup>2</sup>, Jeffrey Seow<sup>2</sup>, Kevin W. Ng<sup>1</sup>, Nicola J. Cook<sup>1</sup>, Chloe Rees-Spear<sup>2</sup>, Mariana Silva dos Santos<sup>1</sup>, James I. MacRae<sup>1</sup>, Marit J. van Gils<sup>4</sup>, George Kassiotis<sup>1</sup>, Laura E. McCoy<sup>3</sup>, Katie J. Doores<sup>2</sup>, Peter Cherepanov<sup>1</sup>

<sup>1</sup>The Francis Crick Institute, London, UK, <sup>2</sup>King's College London, London, UK,

<sup>3</sup>University College London, London, UK, <sup>4</sup>University of Amsterdam, Amsterdam, Netherlands

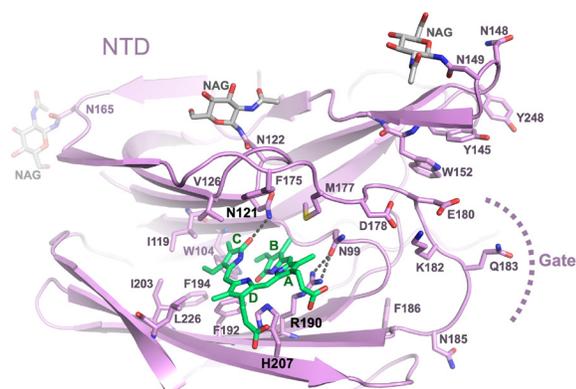
**Background:** Understanding antibody immunity to SARS-CoV-2 and how the virus evades it is of critical importance in the fight against COVID-19. Our best hope of ending the pandemic is antibody-inducing vaccination, yet the precise targets and indeed protective capacity of antibodies remain incompletely

defined. The coronavirus spike is the dominant viral antigen and the target of neutralizing antibodies. We discovered neutralizing epitopes located on the distal face of the SARS-CoV-2 spike N-terminal domain (NTD). Remarkably, instead of glycosylation, the virus uses a surface-exposed loop to restrict the access to this patch, and the gate is controlled through recruitment and dissociation of a metabolite.

**Methods:** Using cryo-electron microscopy and X-ray crystallography we mapped a tetrapyrrole binding site to a deep cleft on the spike N-terminal domain (NTD, Fig. 1) and characterized structural features of a neutralizing epitope controlled by metabolite dissociation.

**Results:** We show that SARS-CoV-2 spike binds biliverdin and bilirubin, the tetrapyrrole products of haem metabolism, with nanomolar affinity in a pH-sensitive manner. At physiological concentrations, biliverdin significantly dampened the reactivity of SARS-CoV-2 spike with immune sera and inhibited a subset of neutralizing antibodies. Access to the tetrapyrrole-sensitive epitope is gated by a flexible loop on the distal face of the NTD. Accompanied by profound conformational changes in the NTD, antibody binding requires relocation of the gating loop, which folds into the cleft vacated by the metabolite.

**Conclusion:** It is well-established that viruses employ extensive glycosylation of their envelopes to shield antibody epitopes. Compared to glycosylation, epitope masking via metabolite recruitment has the advantage of reversibility. For instance, pH-dependence of the spike-tetrapyrrole interaction potentially allows dissociation within the late endosomal compartment. In summary, our results indicate that the virus co-opts the haem metabolite for the evasion of humoral immunity via allosteric shielding of a sensitive epitope and demonstrate the remarkable structural plasticity of the NTD.



**121 BAMLANIVIMAB PREVENTS COVID-19 MORBIDITY AND MORTALITY IN NURSING-HOME SETTING**



**Myron S. Cohen<sup>1</sup>**, Ajay Nirula<sup>2</sup>, Mark Mulligan<sup>3</sup>, Richard Novak<sup>4</sup>, Mary Marovich<sup>5</sup>, Alexander Stemer<sup>6</sup>, Andrew C. Adams<sup>2</sup>, Andrew E. Schade<sup>2</sup>, Jack Knorr<sup>2</sup>, Jay L. Tuttle<sup>2</sup>, Janelle Sabo<sup>2</sup>, Paul Klekotka<sup>2</sup>, Lei Shen<sup>2</sup>, Daniel M. Skovronsky<sup>2</sup>, for BLAZE-2 study team (Lilly/NIH/CoV-19)

<sup>1</sup>Institute of Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>Eli Lilly and Company, Indianapolis, IN, USA, <sup>3</sup>New York University Langone Vaccine Center, Division of Infectious Diseases and Immunology, New York University Grossman School of Medicine, New York, NY, USA, <sup>4</sup>University of Illinois College of Medicine, Chicago, IL, USA, <sup>5</sup>Vaccine Research Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, <sup>6</sup>Indiana University School of Medicine, Gary, IN, USA

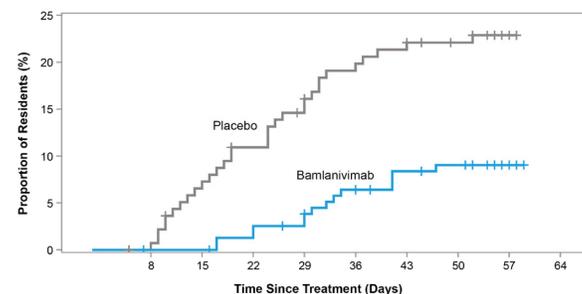
**Background:** The COVID-19 pandemic has disproportionately affected residents of skilled nursing and assisted living facilities. Interventions are urgently needed to protect this vulnerable population. Bamlanivimab is a potent neutralizing monoclonal antibody that binds the receptor-binding domain of the spike protein of SARS-CoV-2. This study evaluates the safety and efficacy of bamlanivimab in preventing COVID-19.

**Methods:** BLAZE-2 is a Phase 3, randomized, double-blind, placebo-controlled, single-dose study that enrolled residents and staff at skilled nursing and assisted living facilities reporting at least one confirmed SARS-CoV-2 case. Eligible participants received bamlanivimab (4200 mg) or placebo intravenously. Nasal swabs were collected at baseline and weekly through day 57 to determine SARS-CoV-2 infection status via reverse transcriptase polymerase chain reaction (RT-PCR). COVID-19-related symptoms and signs were recorded daily. The

primary analysis prevention population included participants negative at baseline for SARS-CoV-2 by RT-PCR and serology. The primary endpoint was incidence of mild or worse COVID-19 by day 57.

**Results:** Of the 1175 participants dosed, 966 (82.2%) comprised the prevention population. The prevention population included 299 residents for whom the median age was 76 years (range 31-104), 234 (78.3%) were aged ≥65, and 178 (59.5%) were female. All were considered at high risk for development of severe COVID-19. The proportion of residents in the prevention population with mild or worse COVID-19 by day 57 was significantly lower in the bamlanivimab group compared with the placebo group (odds ratio [OR], 0.20; 95% confidence interval [CI], 0.08 to 0.49; p<0.001) (Figure). For this same group, bamlanivimab was associated with significant reductions in the incidence of moderate or worse COVID-19 by day 57 (OR, 0.20; 95% CI, 0.08 to 0.49; p<0.001) and incident SARS-CoV-2 infection by day 29 (OR, 0.23; CI, 0.11 to 0.48; p<0.001) compared with placebo. Of the 16 deaths reported during the study, all 5 that were attributed to COVID-19 were in the placebo group. The incidence of both adverse events and serious adverse events were balanced between the bamlanivimab and placebo group.

**Conclusion:** Bamlanivimab was highly effective in reducing the incidence of symptomatic COVID-19 and SARS-CoV-2 infection and was well tolerated. These findings demonstrate the potential beneficial impact of bamlanivimab use on COVID-19 morbidity and mortality among skilled nursing facility residents.



**Figure.** Time since treatment to development of mild or worse COVID-19 with bamlanivimab versus placebo in residents. Residents were SARS-CoV-2 RT-PCR negative and serology negative at baseline. Mild or worse COVID-19 was defined as positive for SARS-CoV-2 by RT-PCR and reporting of mild or worse symptoms and signs associated with COVID-19 within 21 days of detection.

**122 BAMLANIVIMAB+ETESEVIMAB FOR TREATMENT OF COVID-19 IN HIGH-RISK AMBULATORY PATIENTS**



**Michael Dougan<sup>1</sup>**, Ajay Nirula<sup>2</sup>, Robert L. Gottlieb<sup>3</sup>, Masoud Azizad<sup>4</sup>, Bharat Mocherla<sup>5</sup>, Peter Chen<sup>6</sup>, Gregory Huhn<sup>7</sup>, Andrew C. Adams<sup>2</sup>, Andrew E. Schade<sup>2</sup>, Janelle Sabo<sup>2</sup>, Dipak R. Patel<sup>2</sup>, Paul Klekotka<sup>2</sup>, Lei Shen<sup>2</sup>, Daniel M. Skovronsky<sup>2</sup>, for BLAZE-1 Investigators

<sup>1</sup>Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, <sup>2</sup>Eli Lilly and Company, Indianapolis, IN, USA, <sup>3</sup>Baylor University Medical Center and Baylor Scott and White Research Institute, Dallas, TX, USA, <sup>4</sup>Valley Clinical Trials, Northridge, CA, USA, <sup>5</sup>Las Vegas Medical Research Center, Las Vegas, NV, USA, <sup>6</sup>Department of Medicine, Women's Guild Lung Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA, <sup>7</sup>Cook County Health, Chicago, IL, USA

**Background:** Patients with underlying medical conditions have a greater risk of developing severe COVID-19. Unlike vaccine-derived immunity which develops over time, administration of neutralizing monoclonal antibodies is an immediate, passive humoral immunotherapy, with the potential to reduce disease progression, emergency room visits, hospitalizations, and death.

**Methods:** In this phase 3 portion of the BLAZE-1 trial, a high-risk ambulatory cohort of 1035 patients with mild-to-moderate COVID-19 were randomly assigned 1:1 to receive a single intravenous infusion of a neutralizing monoclonal antibody combination treatment consisting of 2800mg bamlanivimab+2800mg etesevimab together, or placebo, within 3 days of laboratory diagnosis. The primary outcome was overall patient clinical status, measured by the proportion of patients who experienced COVID-19-related hospitalization or death by any cause by Day 29.

**Results:** 1035 patients were randomized and infused (mean age [SD]; 53.8 years [16.8], female (52%)). A 70% reduction in COVID-19-related hospitalization and death by any cause by Day 29 was observed in patients who received the bamlanivimab+etesevimab combination treatment (11/518 arm total) compared to those who received placebo (36/517 arm total) ( $\Delta$ [95% CI]= -4.8[-7.4, -2.3])(p=0.0004). No deaths were observed among patients

who received the combination treatment, 10 deaths were reported in the placebo group, at least 8 designated COVID-19-related. A significantly greater reduction in  $\log_{10}$  (viral load) from baseline at Day 7 was observed amongst patients who received bamlanivimab+etesevimab compared to placebo ( $\Delta$ [95% CI]=-1.20[-1.46,-0.94])( $p<0.00000001$ ). The median time to sustained symptom resolution was shorter for those who received the combination treatment (days [95% CI]=8[7.0,8.0]) compared to those who received placebo (days [95% CI]=9[8.0,10.0])( $p=0.007$ ). Similar rates of adverse events were observed between placebo (60/517,11.6%) and combination treatment groups (69/518,13.3%).

**Conclusion:** 2800mg bamlanivimab+2800mg etesevimab neutralizing monoclonal antibody combination therapy significantly reduced COVID-19-related hospitalizations and deaths amongst high-risk ambulatory patients and accelerated the decline in viral load and disease symptoms over time. This study confirms that early intervention with bamlanivimab + etesevimab greatly improves the clinical outcomes for high-risk ambulatory patients, and links reduction in nasopharyngeal viral load to clinically meaningful benefits.

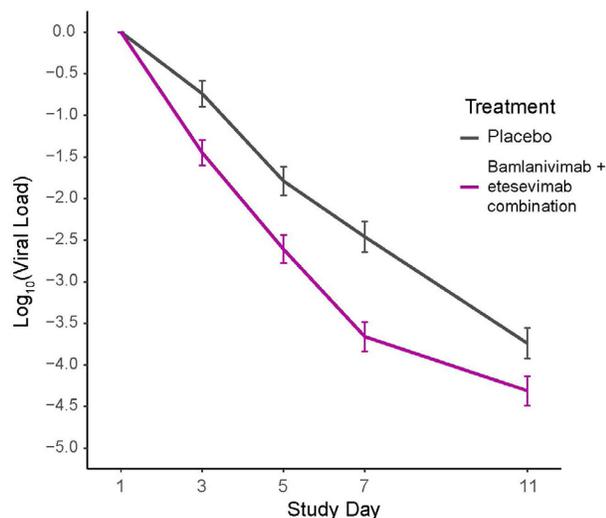


FIGURE: Bamlanivimab + etesevimab combination treatment effect on viral load (Days 1-11). Mean change in viral load ( $\log_{10}$  scale) from baseline to Day 11 following bamlanivimab + etesevimab combination therapy versus placebo. Error bars represent 95% confidence intervals.

### 123 CASIRIVIMAB WITH IMDEVIMAB ANTIBODY COCKTAIL FOR COVID-19 PREVENTION: INTERIM RESULTS



**Meagan P. O'Brien<sup>1</sup>**, Eduardo Forleo Neto<sup>1</sup>, Kuo-Chen Chen<sup>1</sup>, Flonza Isa<sup>1</sup>, Ingeborg Heirman<sup>1</sup>, Neena Sarkar<sup>1</sup>, Divya Ramesh<sup>1</sup>, Myron S. Cohen<sup>2</sup>, Ruanne Barnabas<sup>3</sup>, Christopher B. Hurt<sup>2</sup>, Dan H. Barouch<sup>4</sup>, Katharine J. Bar<sup>5</sup>, Gary Herman<sup>1</sup>, George D. Yancopoulos<sup>1</sup>, David M. Weinreich<sup>1</sup>

<sup>1</sup>Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>University of Washington, Seattle, WA, USA, <sup>4</sup>Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA, <sup>5</sup>University of Pennsylvania, Philadelphia, PA, USA

**Background:** Passive immunization has a long history for infection prevention following exposure. We report results of a descriptive interim analysis from a study of an antibody "cocktail" of casirivimab with imdevimab (cas/imdev; formerly REGN-COV2) designed to bind non-competing epitopes of the viral spike protein, as a potential passive vaccine for the prevention of COVID-19 in people at risk of infection from household contact.

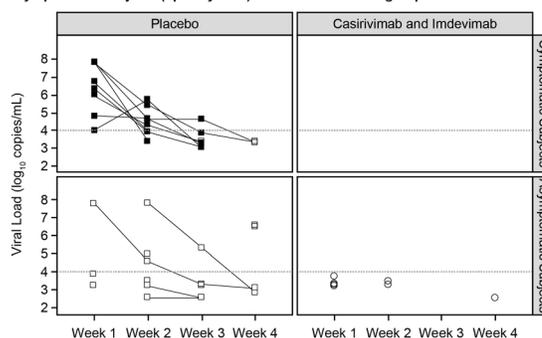
**Methods:** In this ongoing Phase 3 study, asymptomatic participants exposed to a COVID-19-infected household member were randomized 1:1 to placebo or 1200 mg cas/imdev (600 mg of each antibody administered subcutaneously) within 96 hours of their household member testing positive. The analysis included participants who tested negative for SARS-CoV-2 by nasal, saliva, or nasopharyngeal swab and who were seronegative to SARS-CoV-2 antibodies at baseline. The proportion of participants who developed an RT-PCR-confirmed SARS-CoV-2 infection (asymptomatic or symptomatic) during the 1-month efficacy assessment period was summarized.

**Results:** Initial results from the first evaluable 223 placebo and 186 cas/imdev participants who completed  $\geq 29$  days of the study are reported. Reduction

in PCR-positive symptomatic disease was 100% (0/186 cas/imdev vs 8/223 placebo; OR 0.00 [CI 0.00, 0.69]). Reduction in any PCR-positive infection (symptomatic or asymptomatic) was 48% (10/186 vs 23/223; OR 0.49 [CI 0.20, 1.12]). Placebo-group participants had on average 100-fold higher peak viral load. In the cas/imdev group, viral RNA was not detected for longer than 1 week but was detected for 3-4 weeks in approximately 40% of placebo participants (Fig. 1). The proportions of infected participants with high viral loads ( $>10^4$  copies/mL) were 13/21 placebo vs 0/9 cas/imdev. Total weeks of viral RNA detection and high viral load were 44 and 22 weeks in the placebo group vs 9 and 0 in the cas/imdev group. Total symptomatic weeks were 21 for placebo vs 0 for cas/imdev. A similar proportion of participants experienced at least 1 serious adverse event: placebo, 3/222 and cas/imdev, 1/186; none were deemed related to study treatment. Injection site reactions were similar: placebo, 1.4%; cas/imdev, 2.6%.

**Conclusion:** In this descriptive interim analysis of participants at risk of SARS-CoV-2 infection from household transmission, a subcutaneous dose of the cas/imdev antibody cocktail prevented symptomatic infection, reduced overall infection, and decreased viral load and duration of viral RNA detection.

Figure 1. Weekly viral load for individual symptomatic subjects (filled symbol) and asymptomatic subjects (open symbol) in the two treatment groups.



### 124 POTENT NEUTRALIZING ANTIBODIES FOR SEVERE COVID-19: A RANDOMIZED CLINICAL TRIAL

**Carljin Jordans<sup>1</sup>**, Arvind Gharbharan<sup>1</sup>, Corine H. Geurts van Kessel<sup>1</sup>, Jeroen J. Van Kampen<sup>1</sup>, Barry Rockx<sup>1</sup>, Bart Haagmans<sup>1</sup>, Francis Swaneveld<sup>1</sup>, Yvonne Mueller<sup>1</sup>, Peter Katsikis<sup>1</sup>, Marion Koopmans<sup>1</sup>, Bart J. Rijnders<sup>1</sup>, Casper Rockx<sup>1</sup>, for the CONCOVID Trial Network

<sup>1</sup>Erasmus University Medical Center, Rotterdam, Netherlands

**Background:** Convalescent plasma could be an inexpensive and widely available drug for COVID-19 patients. Reports on its effectiveness are inconclusive. We collected convalescent plasma with high titers of neutralizing anti-SARS-CoV-2 antibodies effectively blocking SARS-CoV-2 infection and assessed their clinical and viro-immunological responses in COVID-19 patients with severe disease.

**Methods:** In a multicentre open-label randomized clinical trial in 14 secondary and academic hospitals in the Netherlands, included patients were admitted for COVID-19 with SARS-CoV-2 detected by PCR and not on mechanical ventilation for  $>96$  hours. Convalescent plasma donors were selected based on SARS-CoV-2 plaque reduction neutralization test (PRNT50) result of  $\geq 1:80$ . Primary outcome was day 60 mortality. Secondary outcomes were disease severity, inflammatory and virological markers.

**Results:** Included patients were 72% male, median 63 years (IQR 56-74) and with median 10 days of symptoms (IQR 6-15) at inclusion when they were randomized to convalescent plasma or standard of care. We found no significant difference in mortality at day 60 by using 300mL of convalescent plasma (median PRNT50 1:640) between the arms after adjustment (OR: 0.95, 95%CI: 0.20-4.67). Improvements in WHO COVID-19 disease severity scores at day 15 (OR: 1.30, 95%CI 0.52-3.32) and time to discharge (HR: 0.88, 95%CI: 0.49-1.60) were also comparable. The vast majority of patients already had potent neutralizing anti-SARS-CoV-2 antibodies at hospital admission and at comparable titers as the carefully selected plasma donors. No effect of convalescent plasma on viral clearance in the respiratory tract, anti-SARS-CoV-2 antibody development or changes in serum pro-inflammatory cytokine levels were observed. After the inclusion of 86 patients and per DSMB recommendation, we decided to interrupt the study for futility.

**Conclusion:** Convalescent plasma treatment in this patient group did not improve survival or disease course, nor did it alter relevant virological and immunological parameters. Together, these data indicate that the variable effectivity observed in trials on convalescent plasma for COVID-19 may be explained by the timing of treatment and varying levels of preexisting anti-SARS-CoV-2 immunity in patients. It also substantiates that convalescent plasma should be studied as early as possible in the disease course or at least preceding the start of an autologous humoral response. (Clinicaltrials.gov: NCT04342182)

## 125 ESTIMATING WITHIN-HOST R0 FOR SARS-CoV-2 AND IMPLICATIONS FOR ANTIVIRAL THERAPY

Ruian Ke<sup>1</sup>, Ruy M. Ribeiro<sup>1</sup>, Alan S. Perelson<sup>1</sup>

<sup>1</sup>Los Alamos National Laboratory, Los Alamos, NM, USA

**Background:** The within-host reproductive number R0 is an important parameter to predict the minimum antiviral efficacy needed to suppress viral infection. However, this parameter has not been well quantified for SARS-CoV-2. This is because accurate estimation of this quantity requires longitudinal viral load measurements during the initial phase of infection, when the virus population expands before the viral load peak; yet, most available measurements are made after the viral load peak.

**Methods:** We constructed viral dynamic models to describe a set of longitudinal viral load data from a study where individuals were tested frequently such that viral loads during the viral expansion phase were measured. We fit multiple models to data from a total of 42 infected individuals (14 symptomatic and 28 asymptomatic) to estimate R0 and used a model linking within-host viral load to the infectiousness of a person to evaluate the infectiousness of asymptomatic individuals compared to symptomatic individuals.

**Results:** We estimated that the within-host R0 is between 8-16 across the 48 individuals. This suggests that antiviral efficacy has to be greater than 95% to suppress virus infection in a majority of individuals. The estimated R0 in asymptomatic individuals is lower than in symptomatic individuals (mean 10.0 vs. 13.8; p-value < 0.0001). Our model suggests there exists large heterogeneity in infectiousness among individuals, and asymptomatic individuals may be on average 15% less infectious than symptomatic individuals (p-value = 0.02), not considering isolation measures.

**Conclusion:** An antiviral efficacy of 95% or more is needed to suppress viral infection in most infected individuals. Asymptomatic individuals may be slightly less infectious than symptomatic individuals.

## 126 PHASE IIA PROOF-OF-CONCEPT TRIAL OF NEXT-GENERATION MATURATION INHIBITOR GSK3640254

Christoph Spinner<sup>1</sup>, Franco B. Felizarta<sup>2</sup>, Giuliano Rizzardini<sup>3</sup>, Patrick Philibert<sup>4</sup>, Essack Mitha<sup>5</sup>, Pere Domingo<sup>6</sup>, Christoph Stephan<sup>7</sup>, Michelle DeGrosky<sup>8</sup>, Veronica Bainbridge<sup>9</sup>, Joyce Zhan<sup>10</sup>, Teodora Pene Dumitrescu<sup>10</sup>, Jerry L. Jeffrey<sup>11</sup>, Samit R. Joshi<sup>8</sup>, Max Lataillade<sup>8</sup>, for 208132 Study Team

<sup>1</sup>Technical University of Munich, Munich, Germany, <sup>2</sup>Office of Franco Felizarta, Bakersfield, CA, USA, <sup>3</sup>ASST Fatebenefratelli, Milan, Italy, <sup>4</sup>Hôpital Européen de Marseille, Marseille, France, <sup>5</sup>Newtown Clinical Research, Johannesburg, South Africa, <sup>6</sup>Hospital Santa Creu y Sant Pau, Barcelona, Spain, <sup>7</sup>Universitätsklinikum Frankfurt, Frankfurt, Germany, <sup>8</sup>ViiV Healthcare, Branford, CT, USA, <sup>9</sup>GlaxoSmithKline, Uxbridge, UK, <sup>10</sup>GlaxoSmithKline, Collegeville, PA, USA, <sup>11</sup>ViiV Healthcare, Research Triangle Park, NC, USA

**Background:** Drug resistance and toxicities with HIV-1 regimens can result in treatment failure, so antiretroviral agents with new mechanisms of action are needed. GSK3640254 (GSK'254) is a novel, next-generation HIV-1 maturation inhibitor with pharmacokinetics (PK) to support unboosted, once-daily therapy and a desirable drug-drug interaction profile.

**Methods:** This phase IIA double-blind (sponsor unblinded), randomized, placebo-controlled, adaptive study evaluated the antiviral effect, safety, tolerability, and PK of once-daily GSK'254 administered with a moderate-fat meal in treatment-naïve adults infected with HIV-1. In part 1, participants received GSK'254 10 or 200 mg for 10 days. In part 2, participants received GSK'254 40, 80, or 140 mg for 7 days, modified from 10 days by a protocol amendment to decrease potential for treatment-emergent resistance-associated mutations (RAMs) observed after 7 days in part 1. Primary endpoint was maximum change in plasma HIV-1 RNA during parts 1 and 2. Secondary endpoints were safety, tolerability, and PK parameters.

**Results:** Of 34 participants who received GSK'254 (n=6/dose) or placebo (n=4), 94% were men; mean age was 31.8 years. Mean changes in plasma HIV-1 RNA ranged from -2.0 to 0.2 log<sub>10</sub>; the largest decreases of 2.0- and 1.5 log<sub>10</sub> occurred in the 200- and 140-mg groups, respectively (Table). PK results were generally dose proportional and consistent with those observed in non-HIV-infected individuals. 4/6 participants in the 200-mg group (part 1) developed RAMs on Day 11; 1 of these 4 developed phenotypic resistance. No RAMs were observed at any dose in part 2. No deaths were reported. Two non-drug-related serious adverse events (AEs) of congestive cardiomyopathy and anal abscess occurred. No AEs led to discontinuation. AEs were reported by 22 (65%) participants, with the most common being headache (n=4). Drug-related gastrointestinal AEs, including diarrhea (n=3), abdominal pain (n=2), and vomiting (n=2), occurred in 6 (18%) participants. All AEs and serious AEs were mild to moderate in intensity, except for 1 participant who developed congestive cardiomyopathy and myocarditis (both G).

**Conclusion:** This short-term monotherapy study established a dose-antiviral response relationship. Regardless of dosing duration, GSK'254 140- and 200-mg doses demonstrated greatest declines in plasma HIV-1 RNA. No safety or tolerability concerns were noted. These results support the ongoing phase IIb study (ClinicalTrials.gov identifier: NCT04493216).

Table. Change From Baseline to Study Visit 6 and Nadir in Plasma HIV-1 RNA

| Plasma HIV-1 RNA (log <sub>10</sub> , mean (SD)) | Part 1              |                      |               | Part 2 <sup>a</sup> |                     |                      |               |
|--|---------------------|----------------------|---------------|---------------------|---------------------|----------------------|---------------|
|  | GSK'254 10 mg (N=6) | GSK'254 200 mg (N=6) | Placebo (N=2) | GSK'254 40 mg (N=6) | GSK'254 80 mg (N=6) | GSK'254 140 mg (N=6) | Placebo (N=2) |
| Baseline   | 4.19 (0.311)        | 4.82 (0.476)         | 4.24 (0.417)  | 4.67 (0.233)        | 4.43 (0.510)        | 4.53 (0.577)         | 4.75 (1.782)  |
| Primary endpoint                                 | -0.22 (0.309)       | -1.96 (0.337)        | 0.14 (0.134)  | -1.18 (0.436)       | -1.02 (0.330)       | -1.45 (0.235)        | 0.15 (0.226)  |
| Nadir  | -0.36 (0.252)       | -2.01 (0.329)        | -0.21 (0.262) | -1.18 (0.436)       | -1.02 (0.33)        | -1.49 (0.27)         | -0.03 (0.127) |

GSK3640254, GSK'254. <sup>a</sup>Assessments on Days 10 to 12 are excluded from nadir calculation due to administration of combination ART from Day 8 in part 2.

## 127 POTENT ANTIVIRAL ACTIVITY OF LENACAPAVIR IN PHASE 2/3 IN HEAVILY ART-EXPERIENCED PWH

Sorana Segal-Maurer<sup>1</sup>, Antonella Castagna<sup>2</sup>, Mezgebe Berhe<sup>3</sup>, Gary Richmond<sup>4</sup>, Peter J. Ruane<sup>5</sup>, Gary I. Sinclair<sup>6</sup>, Krittaecho Siripassorn<sup>7</sup>, Ya-Pei Liu<sup>8</sup>, Nicolas Margot<sup>8</sup>, Hadas Dvory-Sobol<sup>8</sup>, Robert H. Hyland<sup>8</sup>, Martin Rhee<sup>8</sup>, Jared Baeten<sup>8</sup>, Diana Brainard<sup>8</sup>, Edwin DeJesus<sup>9</sup>

<sup>1</sup>New York-Presbyterian Queens, Flushing, NY, USA, <sup>2</sup>Ospedale San Raffaele, Milano, Italy, <sup>3</sup>Texas Infectious Diseases Consultants, Dallas, TX, USA, <sup>4</sup>Gary J Richmond, MD, PA, Fort Lauderdale, FL, USA, <sup>5</sup>Ruane Clinical Research Group, Los Angeles, CA, USA, <sup>6</sup>Prism Health North Texas, Dallas, TX, USA, <sup>7</sup>Bamrasnaradura Infectious Diseases Institute, Bangkok, Thailand, <sup>8</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>9</sup>Orlando Immunology Center, Orlando, FL, USA

**Background:** Lenacapavir (LEN, GS-6207), the long-acting first-in-class HIV capsid inhibitor, is in clinical development for the treatment and prevention of HIV-1 infection. With its novel mechanism of action, LEN is fully active in vitro against HIV-1 strains resistant to the major antiretroviral (ARV) classes.

**Methods:** We conducted a Phase 2/3, randomized, double-blind, placebo (PBO)-controlled study in heavily treatment-experienced (HTE) people with HIV (PWH) failing their current regimen with HIV-1 RNA (VL) ≥ 400 c/mL and documented resistance to ≥ 2 agents from ≥ 3 of the 4 major ARV classes. Participants were randomized (2:1) to add LEN or PBO to their failing regimen for 2 weeks. During this functional monotherapy period, LEN or PBO was given orally (600 mg on Day [D] 1 and 2 and 300 mg on D8). The primary efficacy endpoint was the proportion of participants with at least 0.5 log<sub>10</sub> c/mL decline in VL by D15. At D15, those on oral LEN received subcutaneous (SC) LEN 927 mg (q6month), while those on PBO started the LEN 2-week oral lead-in, followed by q6month SC. All participants initiated an investigator-selected, optimized background regimen (OBR) at D15. Here we report complete data for the functional monotherapy period and preliminary data for the LEN+OBR period.

**Results:** 36 participants were randomized: 28% were female and 46% Black. Median age was 54 years. Mean baseline VL was 4.27 log<sub>10</sub> c/mL. At D15, 88% of participants on LEN (21 of 24) had at least 0.5 log<sub>10</sub> c/mL decline compared to 17% on PBO (2 of 12) (difference: 71%, 95% CI 35 to 90%, p < 0.0001). The median (range) change in VL (log<sub>10</sub> c/mL) was -2.00 (-3.29 to -0.29) vs -0.08 (-1.93 to 0.31). During the LEN + OBR period at 4 weeks after SC dosing, 58%

(21 of 36) had VL <50 c/mL. One participant with no fully active agent in OBR had emergent resistance to LEN but later re-suppressed while on LEN after adding TAF. The median (range) duration of follow up on LEN was 26 (7–46) weeks. There were no serious adverse events (AEs) related to study drug, discontinuations due to AEs, or deaths. The most frequent AEs (any grade) were injection site swelling (28%) and nodule (25%). Injection site reactions related to LEN (50%) were all mild or moderate. Longer term data will be reported.

**Conclusion:** LEN led to a rapid and clinically relevant decline in VL when added to a failing regimen in HTE PWH. LEN was generally safe and well-tolerated. These results support the ongoing evaluation of LEN for the treatment and prevention of HIV-1 infection.

## 128 ACTIVITY AND RESISTANCE CHARACTERIZATION OF THE HIV CAPSID INHIBITOR LENACAPAVIR

Christian Callebaut<sup>1</sup>, Laurie VanderVeen<sup>1</sup>, Nicolas Margot<sup>1</sup>, Vidula Naik<sup>1</sup>, Martin Rhee<sup>1</sup>

<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Lenacapavir (LEN) in vitro resistance selections identified resistance associated mutations (RAMs) in HIV-1 capsid (CA) associated with reduced susceptibility (L56I, M66I, Q67H, K70N, N74D, N74S, and T107N). Characterization of mutants in single-cycle (SC) assays indicated that most of these RAMs were associated with reduced replication capacity (RC). We studied LEN antiviral activity in isolates containing LEN-RAMs in SC and multi-cycle (MC) assays to determine their impact on RC across several assay formats and to explore their potential cross-resistance with protease inhibitors (PIs). In addition, the activity of LEN was determined in previously untested HIV-1 subtypes.

**Methods:** Mutations were inserted in the pXXLAI proviral clone by site-directed mutagenesis; replicative viruses were generated by transfection. Viruses (6 single- and 4 double-mutants) were tested in 2 different MC formats to determine susceptibility to LEN and controls. Mutated sequences were used to generate SC test vectors that were tested in a Gag-Pro assay, along with isolates with diverse HIV-1 subtypes (A, A1, AE, AG, B, BF, C, D, G, and H) (Monogram).

**Results:** Antiviral activity and susceptibility in the SC assay confirmed the previously observed data, with Q67H leading to a 4.6-fold reduction in susceptibility to LEN and 58% RC in comparison with wild-type (WT); M66I showed a >2000-fold reduction in susceptibility and 1.5% RC. Although LEN susceptibility data were obtained for all 10 mutants in the SC assay, in the more restrictive MC assay, data were only obtained for 6 of the 10 mutants, with 4 lacking measurable infectivity in the assay, particularly the M66I and M66I + Q67H mutants. Overall, LEN susceptibility values in the MC assay were similar to those in the SC assay. Susceptibility to the PIs darunavir and atazanavir was unchanged from WT in the SC and MC assays. LEN showed similar potency across diverse subtypes in the SC assay, with EC<sub>50</sub> values (range: 124 – 357 pM) on par with that of the WT control (290 pM).

**Conclusion:** Susceptibility to LEN in single-cycle and multi-cycle assay formats has expanded our understanding of LEN resistance in vitro and confirmed the decreased RC of the mutant viruses. In addition, mutants with resistance to LEN were found not cross-resistant to PIs, and LEN susceptibility was similar across isolates with diverse subtypes. These data emphasize the beneficial profile of LEN as a potential treatment option for people living with HIV.

## 129 RESISTANCE PROFILE OF MK-8507, A NOVEL NNRTI SUITABLE FOR WEEKLY ORAL HIV TREATMENT

Tracy L. Diamond<sup>1</sup>, Ming-Tain Lai<sup>1</sup>, Meizhen Feng<sup>1</sup>, Min Xu<sup>1</sup>, Nancy A. Sachs<sup>1</sup>, Daria Hazuda<sup>1</sup>, Ernest Asante-Appiah<sup>1</sup>, Jay A. Grobler<sup>1</sup>

<sup>1</sup>Merck & Co, Inc, West Point, PA, USA

**Background:** MK-8507 is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) in clinical development as a once-weekly oral treatment for HIV-1 infection. To support the development of MK-8507, in vitro assays were performed to assess its virologic profile and compare its activity to clinically approved NNRTIs.

**Methods:** Half-maximal inhibitory concentration (IC<sub>50</sub>) of MK-8507 against wild-type subtype B (WT) HIV-1 was assessed in a multiple cycle assay. Activity against clinical variants representing multiple HIV-1 subtypes was determined using the PhenoSense<sup>®</sup> assay. MK-8507 was evaluated in two-drug combination antiviral and cytotoxicity assays with each of 17 antiviral agents across mechanistic classes. Viral resistance selection studies with escalating concentrations of MK-8507 were conducted on cells infected with HIV-1 subtype

A, B, or C to determine pathways to MK-8507 resistance. Antiviral activity of MK-8507 on common NNRTI resistance-associated variants and a panel of variants that emerged under MK-8507 selective pressure was determined in multiple cycle assays. Activity against a panel of clinical NNRTI resistance-associated variants was determined by PhenoSense<sup>®</sup>.

**Results:** MK-8507 had an IC<sub>50</sub> of 51.3 nM against WT HIV-1 and maintained similar activity across HIV-1 subtypes. It displayed additive antiviral activity and was not antagonistic in combination with all antiretrovirals tested, including islatravir. In resistance selection experiments V106A was the primary mutation observed with subtype B virus and V106M was the primary mutation observed with subtypes A and C. Most other mutations observed (E138K, H221Y, Y188L, P225H, F227C/L, m<sub>3</sub>30L, L234I, P236L, Y318F) were in combination with V106A/M mutations. Variants observed in vitro under MK-8507 selective pressure are uncommon in the clinic (prevalence <2% in the Stanford HIV Drug Resistance Database). MK-8507 had potency reductions from 0.9 to 544.0-fold against variants that emerged in selection experiments and had <5 fold-shifts against common NNRTI resistance-associated variants, K103N, Y181C, and G190A. It also maintained <5-fold shift against 13 of 21 clinical NNRTI variants tested in the PhenoSense<sup>®</sup> assay.

**Conclusion:** MK-8507 is a novel and potent NNRTI with activity against common NNRTI resistance-associated variants and has antiviral activity and a resistance profile similar to doravirine and distinct from efavirenz. This in vitro profile supports further development of MK-8507 as a component of a once weekly regimen.

## 130 RIFAPENTINE +/- MOXIFLOXACIN FOR PULMONARY TUBERCULOSIS IN PEOPLE WITH HIV

April Pettit<sup>1</sup>, Payam Nahid<sup>2</sup>, Patrick P. Phillips<sup>2</sup>, Andrew Vernon<sup>3</sup>, Ekaterina Kurbatova<sup>3</sup>, Rodney Dawson<sup>4</sup>, Ian Sanne<sup>5</sup>, Ziyaad Waja<sup>6</sup>, Lerato Mohapi<sup>6</sup>, Wadzanai Samaneka<sup>7</sup>, John Johnson<sup>8</sup>, Susan Dorman<sup>9</sup>, Richard E. Chaisson<sup>10</sup>, Susan Swindells<sup>11</sup>, for TBTC Study 31/ACTG 5349 study team

<sup>1</sup>Vanderbilt University, Nashville, TN, USA, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA, <sup>3</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>4</sup>University of Cape Town, Cape Town, South Africa, <sup>5</sup>University of Witwatersrand, Johannesburg, South Africa, <sup>6</sup>Perinatal HIV Research Unit, Soweto, South Africa, <sup>7</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>8</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>9</sup>Medical University of South Carolina, Charleston, SC, USA, <sup>10</sup>Johns Hopkins University, Baltimore, MD, <sup>11</sup>University of Nebraska Medical Center, Omaha, NE, USA

**Background:** Daily regimens with rifapentine (RPT) and moxifloxacin (MOX) have potent antimicrobial activity that may allow treatment shortening for drug-susceptible pulmonary tuberculosis (TB).

**Methods:** TB Trials Consortium Study 31/ACTG A5349 is an international, randomized, open-label, phase 3 non-inferiority (NI) trial comparing two 4-month RPT-based regimens with the 6-month control regimen (NI margin 6.6%). One 4-month regimen replaced rifampin with RPT 1200mg (RPT regimen); the other replaced both rifampin with RPT 1200mg and ethambutol with MOX 400 mg (RPT-MOX regimen). The primary endpoints were TB disease-free survival 12 months after randomization for efficacy and grade 3 or higher severe adverse events (AEs) on treatment for safety. Randomization was stratified by cavitory disease and HIV-status; participants with HIV on efavirenz (EFV)-based antiretroviral therapy (ART) were enrolled in a staged fashion, to allow studies of drug-drug interactions between RPT and EFV.

**Results:** We enrolled 2516 participants from 13 countries in sub-Saharan Africa, Asia, and the Americas; median age was 31 years, 71% were male, 64% were non-White, and 73% had cavitory disease. Two hundred fourteen (8%) had HIV infection; median age was 36 years, 59% were male, 99% were non-White, and 72% had cavitory disease. The median CD4+ count was 344 cells/mm<sup>3</sup>, and all were on EFV-based ART at baseline or started within 8 weeks of enrollment. Overall, the RPT-MOX regimen efficacy was non-inferior to control after adjustment for HIV status and cavitation in the microbiologically eligible and assessable populations; absolute difference (AD) 1.0% [95% CI -2.6% to +4.5%] and 2.0% [95% CI -1.1%, 5.1%], respectively. Among participants with HIV, the RPT-MOX regimen was non-inferior to control in the microbiologically eligible population (AD -7.5% [95% CI -20.8% to +6.1%] and assessable population (AD -6.6% [95% CI -18.3% to +5.0%], respectively). A favorable outcome in the assessable analysis population with HIV infection occurred in 53/58 (91%) in the RPT-MOX arm, 48/65 (74%) in the RPT arm, and 50/59 (85%) in the control arm.

Fewer severe or serious AEs were reported in experimental regimens than the control regimen (Table).

**Conclusion:** In people living with HIV, the 4-month daily RPT-MOX regimen had non-inferior efficacy compared to the standard 6-month control regimen and was safe and well-tolerated. This new regimen represents a major milestone in the lengthening of duration of TB treatment regimen.

Table. TBTC S31/ACTG 5349 trial outcomes among participants with HIV

|   | Control arm   | RPT arm       | RPT-MOX arm   | Total           |
|---|---------------|---------------|---------------|-----------------|
| <b>Primary efficacy outcomes (N with favorable outcome / Total in analysis [%])</b> |               |               |               |                 |
| Microbiologically eligible  | 50/64 (78.1%) | 48/68 (70.6%) | 53/62 (85.5%) | 151/194 (77.8%) |
| Assessable*   | 50/59 (84.8%) | 48/65 (73.9%) | 53/58 (91.4%) | 151/182 (83.0%) |
| Per Protocol 95#  | 44/45 (97.8%) | 41/52 (78.9%) | 43/45 (95.6%) | 128/142 (90.1%) |
| <b>Safety outcomes (N with adverse event / Total in safety analysis [%])</b>        |               |               |               |                 |
| Grade 3-5 (severe) AEs on treatment   | 16/70 (22.9%) | 14/71 (19.7%) | 12/72 (16.7%) | 42/213 (19.7%)  |
| Serious AEs on treatment  | 8/70 (11.4%)  | 6/71 (8.5%)   | 2/72 (2.8%)   | 16/213 (7.5%)   |
| Deaths  | 2/70 (2.9%)   | 3/71 (4.2%)   | 0/72 (0.0%)   | 5/213 (2.3%)    |

\* Microbiologically eligible: participants with culture-confirmed TB susceptible to drugs under evaluation  
 \*Assessable: microbiologically eligible participants excluding those who were lost to follow-up with their last culture negative, became pregnant and stopped treatment assignment, died during follow-up, died due to violence/accident during treatment, and/or had TB re-infection.  
 # Per-Protocol 95: assessable participants who completed 95% of study treatment

**131 HIGH-DOSE RIFAMPICIN FOR HIV-ASSOCIATED TB MENINGITIS: A PHASE II RANDOMISED TRIAL**

**Fiona Cresswell**<sup>1</sup>, David Meya<sup>2</sup>, Enock Kagimu<sup>2</sup>, Daniel Grint<sup>1</sup>, Lindsey te Brake<sup>3</sup>, John Kasibante<sup>2</sup>, Emily Martyn<sup>1</sup>, Morris Rutakingirwa<sup>1</sup>, Lillian Tugume<sup>2</sup>, Kenneth Sebambulidde<sup>2</sup>, Elin Svensson<sup>3</sup>, Rob Aarnoutse<sup>3</sup>, Ananta Bangdiwala<sup>4</sup>, Alison Elliott<sup>1</sup>, David Boulware<sup>4</sup>, for Rift study

<sup>1</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>2</sup>Infectious Disease Institute, Kampala, Uganda, <sup>3</sup>Radboud University Medical Center, Nijmegen, Netherlands, <sup>4</sup>University of Minnesota, Minneapolis, MN, USA

**Background:** Tuberculous meningitis (TBM) carries a high case-fatality of ~50% in HIV co-infection. Treatment of TBM is challenging as rifampicin does not readily penetrate into cerebrospinal fluid (CSF) at standard dosing (10mg/kg). High dose rifampicin improves CSF rifampicin levels and survival in predominantly HIV-negative Asian adults with TBM. However, intensified therapy for TBM has not been studied in African adults and there is a paucity of data on safety and pharmacokinetics (PK) of high dose rifampicin in HIV co-infection.

**Methods:** We conducted an open-label phase II trial (ISRCTN42218549) with three arms: A) intravenous rifampicin (20mg/kg/day, IV-20); B) oral rifampicin (35mg/kg/day, PO-35); C) standard of care (rifampicin 10mg/kg/day, SOC). Standard dosing of isoniazid, pyrazinamide, ethambutol were administered. Eligible adults in two Ugandan hospitals underwent PK sampling (0, 2, 4, 8h post-dose) on day two along with a CSF sample. Follow-up was 24-weeks. Standard non-compartmental analysis and population PK modelling determined maximum concentration in serum (C<sub>max</sub>) and total exposure (AUC<sub>0-24</sub>).

**Results:** We randomised 61 adults, 56 (92%) were HIV-positive, median CD4=50 (IQR 46–56) cells/μl. M. tuberculosis in CSF was confirmed by Xpert MTB/Rif Ultra in 31 (51%). Compared to SOC, rifampicin IV-20 and PO-35 significantly increased geometric mean serum exposures: C<sub>max</sub> increased from 6.0mg/l to 36.2mg/l and 29.3mg/l (P<0.001), and AUC<sub>0-24</sub> increased from 42.9mg·h/l to 248.7mg·h/l and 326.9mg·h/l (P<0.001) respectively. In CSF, with SOC, 10/18 (56%) had undetectable rifampicin (<0.25mg/l), geometric mean concentration was 0.27mg/l. CSF concentrations were increased to 1.74mg/l and 2.17mg/l in the IV-20 and PO-35 arms respectively (P<0.001). CSF rifampicin minimal inhibitory concentration (MIC) was reached in 11% of SOC, 93% of IV-20 and 95% of PO-35 adults. High dose rifampicin was safe, with no increase in grade 3-5 adverse events (P=0.74). Drug induced liver injury occurred in 1 (5%), 2 (10%) and 4 (19%) of participants in the IV-20, PO-35 and SOC arms respectively. Overall, 24 (39%) participants died, with no between-arm difference in mortality (P=0.48)

**Conclusion:** With standard TB treatment only 1 in 10 adults with TBM had a CSF rifampicin concentration above the MIC. In a predominantly HIV-positive severely immunocompromised Ugandan population, high dose rifampicin

was safe, resulted in significant increases in plasma and CSF exposures, and attainment of therapeutic CSF levels.

|  | IV-20              | PO-35              | Control                         | P value |
|--|--------------------|--------------------|---------------------------------|---------|
| <b>Serum AUC<sub>0-24</sub> (h·mg/L)</b>               |                    |                    |                                 |         |
| Geometric mean (95% CI)                                | 249 (202 - 306)    | 327 (248 - 430)    | 42.9 (29.2 - 63.0)              | <0.001  |
| Ratio to control                                       | 5.80               | 7.62               | -                               |         |
| P value  | <0.001             | <0.001             | -                               |         |
| n (%) achieving target of ≥300 h·mg/L                  | 7 (36.8)           | 9 (47.4)           | 0 (0%)                          | <0.001  |
| <b>Serum C<sub>max</sub> (mg/l)</b>                    |                    |                    |                                 |         |
| Geometric mean (95% CI)                                | 36.2 (31.8 - 41.2) | 29.3 (23.0 - 37.5) | 6.04 (4.20 - 8.68)              | <0.001  |
| Ratio to control                                       | 5.99               | 4.86               | -                               |         |
| P value  | <0.001             | <0.001             | -                               |         |
| n (%) achieving target of >8mg/L                       | 20 (100)           | 20 (100)           | 10 (47.62)                      | <0.0001 |
| <b>CSF concentration C<sub>0-1</sub> (mg/l)</b>        |                    |                    |                                 |         |
| Geometric mean (95% CI)                                | 1.74 (1.20 - 2.53) | 2.17 (1.64 - 2.86) | 0.27 <sup>b</sup> (0.17 - 0.45) | 0.058   |
| Ratio to control                                       | 6.44               | 8.00               | -                               |         |
| P value  | <0.001             | <0.001             | -                               |         |
| n (%) with detectable CSF level                        | 15 (100)           | 19 (100)           | 8 (44)                          | <0.001  |
| n (%) with concentration above rifampicin MIC (1 mg/L) | 14 (93.3%)         | 18 (94.7%)         | 2 (11.1%)                       | <0.001  |

**132 BICTEGRAVIR CONCENTRATIONS AND VIROLOGIC RESPONSES IN PLWH RECEIVING 1HP FOR LTBI**

**Hsin-Yun Sun**<sup>1</sup>, Chih-Ning Cheng<sup>2</sup>, Ya-Ting Lin<sup>2</sup>, Wen-Chun Liu<sup>3</sup>, Yu-Chung Chuang<sup>3</sup>, Shu-Wen Lin<sup>2</sup>, Ching-Hua Kuo<sup>2</sup>, Chien-Ching Hung<sup>3</sup>

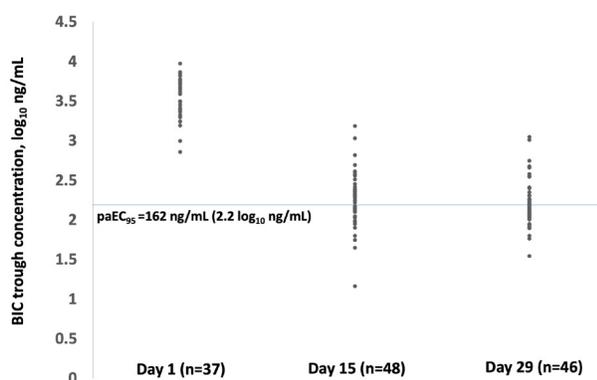
<sup>1</sup>National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, <sup>2</sup>National Taiwan University, Taipei, Taiwan, <sup>3</sup>National Taiwan University Hospital, Taipei, Taiwan

**Background:** One-month regimen of daily rifapentine (600 mg) plus isoniazid (300 mg) (1HP) is an attractive preventive strategy for PLWH with latent TB infection (LTBI). However, the optimal integrase strand transfer inhibitor-based regimens in combination with 1HP remain unknown. We aimed to assess the completion rate, bicittegravir (BIC) trough concentration, cytokine profile, and virologic response in PLWH with LTBI who received 1HP and BIC/FTC/TAF concurrently.

**Methods:** PLWH were enrolled who tested positive by interferon gamma release assay (IGRA) and had received BIC/FTC/TAF for at least 2 weeks with plasma HIV RNA load (PVL) <200 copies/mL within 6 months of initiation of 1HP. BIC trough concentrations were determined with the use of LC-MS/MS before the first dose (Day 1), 24 hours after the 14th (Day 15) and 28th (Day 29) doses of 1HP; and PVLs were determined within 6 months before and 2 weeks after 1HP initiation (Day 15), end of 1HP (Day 29), and 3 months after 1HP discontinuation. Cytokine levels were determined with the use of commercial kits on Day 1, Day 15, and Day 29.

**Results:** From November 2019 to November 2020, a total of 1832 PLWH tested for LTBI with 59 (3.2%) being positive by IGRA. Fifty PLWH with LTBI who had received BIC/FTC/TAF for at least 2 weeks were enrolled for 1HP treatment (98% men and 90% MSM). Only one patient (2.0%) discontinued 1HP on Day 15 due to fever and generalized rashes; more than 5-fold increases of the IFN-gamma, IL-6, TNF-alpha, and IL-10 levels were observed. Statistically insignificant increases of the cytokines assessed were observed in the remaining PLWH. Sequential changes of BIC trough concentrations after 1HP initiation were determined in 48 PLWH (Figure). The percentages of BIC trough concentration above the protein-adjusted 95% effective concentration (paEC95=162 ng/mL) were 56.3% on Day 15 and 35.4% on Day 29. PVLs were <200 and <50 copies/mL in 100% and 97.9% of the enrolled PLWH before 1HP initiation (median 20 copies/mL and range 20-85 copies/mL), 91.7% and 72.9% on Day 15 (median 20 copies/mL and range 20-423 copies/mL), 97.9% and 91.5% on Day 29 (median 20 copies/mL, range 20-205 copies/mL), and 100% and 97.7% 3 months after 1HP discontinuation (median PVL 20 copies/mL, range 20-57 copies/mL), respectively.

**Conclusion:** BIC concentrations were significantly decreased with concurrent use of 1HP among PLWH with LTBI.



### 133 A CLUSTER RANDOMIZED TRIAL OF CONTACT TRACING IN HOUSEHOLDS OF INDEX PATIENTS WITH TB

Neil A. Martinson<sup>1</sup>, Limakatso Lebina<sup>1</sup>, Emily Webb<sup>2</sup>, Andrew Ratsela<sup>3</sup>, Jonathan Golub<sup>4</sup>, Zama Bosch<sup>1</sup>, Kegaugetswe P. Motsomi<sup>1</sup>, Peter MacPherson<sup>5</sup>

<sup>1</sup>Perinatal HIV Research Unit, Soweto, South Africa, <sup>2</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>3</sup>University of Limpopo, Polokwane, Limpopo, South Africa, <sup>4</sup>Johns Hopkins Center for TB Research, Baltimore, MD, <sup>5</sup>Liverpool School of Tropical Medicine, Liverpool, UK

**Background:** Household contact tracing and investigation for tuberculosis (TB) is recommended, but has not been widely implemented in high HIV-prevalence settings due to uncertainty over effectiveness and the costs of conducting home visits. Intensive HIV/TB screening with appropriate action could reduce household TB transmission and mortality.

**Methods:** Index TB patients in two health districts of South Africa with markedly different TB and HIV burdens (Mangaung in Free State and Capricorn in Limpopo) were randomised in a stratified manner, in a 1:1 ratio, to receive either an intensive household contact HIV/TB screening with referrals, or standard of care (SoC). In the intensive screening arm, consenting household members received: (1) collecting of sputum for TB testing (Xpert and culture) and point-of-care HIV testing for those without evidence of HIV-infection, with standardized treatment referral for those testing positive for TB and/or HIV; (2) home initiation of TB preventive therapy for HIV-infected individuals, children  $\leq 5$  years old, or tuberculin skin test [TST] positive HIV seronegative individuals; and (3) a supportive household follow-up visit three months later. Index patients randomised to SoC received sufficient standardized referral letters for each of their household contacts without a household visit until the outcome visit. The primary outcome was TB-free survival, measured 15-months after randomization. Secondary outcomes were TST positivity in children  $< 14$  years and prevalence of undiagnosed or untreated HIV.

**Results:** Between December 2016 and March 2019, 1,032 households (4,129 contacts) and 1,030 (4,459 contacts) were randomised to the intervention and SoC arms. At 15-months, the percentage of household members who experienced incident TB or death did not differ between contacts from households that received intensive screening with referral (93/3,230, 2.9%) and those that receive SoC (80/2,600, 3.1%) (hazard ratio 0.90, 0.66-1.24). Prevalence of TST positivity was higher in the intensive screening arm (38/845, 4.5%) compared to the SoC arm (15/800, 1.9%, odds ratio: 2.25, 1.07-4.72). Prevalence of undiagnosed or untreated HIV was similar between arms (41/3185, 1.3% vs. 32/2543, 1.3%; OR 1.02, 0.64-1.64).

**Conclusion:** Despite being widely recommended, we were unable to demonstrate that a comprehensive household contact tracing strategy improved TB-free survival. Provision of contact referral letters to index patients with TB should be promoted over household visit strategies.

134



### A CLUSTER RANDOMIZED TRIAL OF TARGETED UNIVERSAL TESTING FOR TB IN CLINICS

Limakatso Lebina<sup>1</sup>, Bareng A. Nonyane<sup>2</sup>, Ribka Berhanu<sup>3</sup>, Pren Naidoo<sup>4</sup>, Zameer Brey<sup>4</sup>, Anthony Kinghorn<sup>1</sup>, Siphon Nyathi<sup>5</sup>, Katherine Young<sup>6</sup>, Harry Hausler<sup>6</sup>, Lucy Conell<sup>7</sup>, Leisha Genade<sup>1</sup>, Neil A. Martinson<sup>1</sup>, for the TUTT Team

<sup>1</sup>University of the Witwatersrand, Johannesburg, South Africa, <sup>2</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>3</sup>Boston University, Boston, MA, USA, <sup>4</sup>Bill and Melinda Gates Foundation, Seattle, WA, USA, <sup>5</sup>Aquity Innovations, Johannesburg, South Africa, <sup>6</sup>TB/HIV Care Association, Cape Town, South Africa, <sup>7</sup>Right to Care, Johannesburg, South Africa

**Background:** Many patients with tuberculosis (TB) disease are not diagnosed or started on TB treatment. Reliance on TB symptom screening misses patients with TB, especially HIV-infected individuals. We assessed if targeted universal testing for TB (TUTT) in adults at extreme risk of TB would increase the total number of patients diagnosed with TB in primary care clinics.

**Methods:** We conducted a cluster randomised trial, allocating 62 large clinics in three provinces in South Africa to either: augmentation of standard of care (SOC), symptom-based TB testing with the TUTT intervention, or to SOC. In TUTT clinics, we targeted high risk adult ( $\geq 18$  years) clinic attendees, irrespective of the presence of TB symptoms. High risk individuals were: HIV-infected; close contacts of someone with TB in the past year; or prior TB in the past 2 years. Fieldworkers in TUTT clinics collected a sputum sample, which was processed and split for Xpert Ultra and mycobacterial culture. Outcome was the total number of TB patients diagnosed per clinic per month in each arm, measured using counts of laboratory diagnoses of TB at all clinics in the year prior, and during the intervention. We compared numbers of TB cases per month during the intervention between study arms, and also taking into account secular trends.

**Results:** From March 2019 to March 2020, we consented and sputum-tested 30,500 adults in TUTT intervention clinics. Most (71%) were HIV-infected. Overall 8% of all sputum tests were positive for *M. tuberculosis* on  $\geq 1$  assay. There was marked variation in effect of the intervention at individual clinics and by province but cluster- and province-adjusted comparison between TUTT and SoC clinics, restricted to the intervention period, showed a nonsignificant increase of 14% additional patients with TB diagnosed in TUTT clinics per month (95%CI: -6%; +38%). However, difference-in-differences analyses showed TB diagnoses per clinic per month in SoC clinics declined by 8% in the intervention period compared to the year prior, whereas TUTT clinics diagnosed 17% (95%CI: 14%; 19%) more TB patients relative to SoC.

**Conclusion:** Implementing targeted universal testing in high risk groups increased the number of TB patients by 17% compared to symptom-based TB testing, and strategies such as this may assist in eliminating TB.

### 135 A SIMPLE AND SAFE APPROACH TO HCV TREATMENT: FINDINGS FROM THE A5360 (MINMON) TRIAL

Sunil S. Solomon<sup>1</sup>, Sandra Wagner-Cardoso<sup>2</sup>, Laura M. Smeaton<sup>3</sup>, Leonard Sowah<sup>4</sup>, Chanelle Wimbish<sup>5</sup>, Gregory Robbins<sup>6</sup>, Irena Brates<sup>3</sup>, Nelson Cheinquer<sup>7</sup>, Anchalee Avithingsanon<sup>8</sup>, Donald Anthony<sup>9</sup>, Benjamin Linas<sup>10</sup>, Susanna Naggie<sup>11</sup>, David Wyles<sup>12</sup>, Mark S. Sulkowski<sup>1</sup>

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil, <sup>3</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>4</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>5</sup>Social and Scientific Systems, a DLH Company, Silver Spring, MD, <sup>6</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>7</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>8</sup>Thai Red Cross AIDS Research Center, Bangkok, Thailand, <sup>9</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>10</sup>Boston Medical Center, Boston, MA, USA, <sup>11</sup>Duke University Medical Center, Durham, NC, USA, <sup>12</sup>University of Colorado School of Medicine, Aurora, CO, USA

**Background:** To achieve global hepatitis C virus (HCV) elimination by 2030, 80% of the ~71 million people with chronic HCV need to be treated, necessitating simplification of treatment delivery and associated laboratory monitoring without compromising efficacy or safety. The COVID-19 pandemic has further highlighted the need for innovative models that minimize face-to-face contact.

**Methods:** ACTG A5360 is a single-arm, open-label trial to evaluate safety and efficacy of a minimal monitoring (MINMON) approach to HCV therapy in treatment-naïve persons with no evidence of decompensated cirrhosis. All participants received a single-tablet, fixed-dose regimen of sofosbuvir/velpatasvir

for 12 weeks. MINMON included: (1) no genotyping; (2) all tablets dispensed at entry; (3) no on-treatment visits/labs; and (4) two remote contacts at Weeks 4 (adherence assessment) and 22 (scheduling sustained virology response [SVR] visit). Unplanned visits for participant concerns (related/unrelated to an adverse event [AE]) were allowed. SVR is defined as HCV RNA <lower limit of quantification at least 22 weeks after treatment initiation (missing HCV RNA = failure). 95% confidence intervals (CI) for SVR used Wilson's Score.

**Results:** 400 participants were enrolled from 10/2018–07/2019 at 38 sites in five countries across 4 continents; 399 initiated treatment. Median age was 47 years, 138 (35%) were cisgender women, 22 (6%) self-identified across the transgender spectrum, and 166 (42%) were White. At entry, 34 (9%) had compensated cirrhosis (FIB-4 ≥3.25) and 166 (42%) had HIV co-infection. Remote contact was successful at Weeks 4 and 22 for 394 (99%) and 335 (84%) participants, respectively. HCV RNA for SVR was available for 396 participants. Overall, 95% (379/399) achieved SVR (95% CI: 92.4%, 96.7%); SVR by country, biological sex, gender identity, age, cirrhosis status, HIV co-infection status and injection drug use are presented in Figure. Fifteen (3.8%) participants had unplanned visits; 3 were AE related and 6 were related to abnormalities during screening. Serious AE events through Week 24 visit were reported in 14 (3.5%) participants; none were treatment related or resulted in death.

**Conclusion:** In a diverse, global patient population, the MINMON approach to HCV treatment delivery was safe and achieved SVR comparable to current standards. Wider adoption of this approach coupled with innovative case-finding strategies may facilitate HCV elimination while minimizing in-person appointments and resource use.

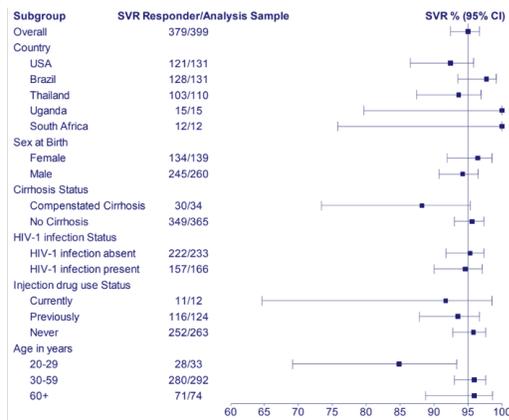


Figure: SVR by select participant characteristics at baseline

or cancer registry. We used multivariable Cox regression to determine adjusted hazard ratios (aHRs [95% confidence intervals]) of factors assessed at cohort entry (age, sex, race, body mass index), ever during observation (hepatitis C coinfection, heavy alcohol use defined as alcohol use disorder diagnosis and/or ≥3 drinks/day or ≥7 drinks/week for females; ≥4 drinks/day or ≥14 drinks/week for males on AUDIT-C), or that were time-updated (HIV RNA, CD4+ cell percentage, diabetes mellitus, HBV DNA, HBV-active antiretroviral therapy [ART]).

**Results:**

Among 8,354 HIV/HBV-coinfected individuals (median age, 43 years; 93% male; 52.4% non-white), 115 HCC cases were diagnosed over 65,392 person-years of follow-up (incidence rate, 1.8 [95% CI, 1.5-2.1] events/1,000 person-years). Independent risk factors for HCC were age ≥40 years (aHR, 2.14 [1.36-3.37]), hepatitis C coinfection (aHR, 1.60 [1.07-2.39]), and heavy alcohol use (aHR, 1.51 [1.03-2.21]), while time-updated HIV RNA >500 copies/mL (aHR, 0.88 [0.55-1.41]) and time-updated CD4+ percentage <14% (aHR, 1.03 [0.56-1.90]) were not. Among the 3,054 who had HBV DNA quantified, the risk of HCC was increased with HBV DNA >200 IU/mL (aHR, 2.70 [1.23-5.93]) and especially at levels >200,000 IU/mL (aHR, 4.34 [1.72-10.94]), see Table. HCC risk was also higher with each 1.0 log<sub>10</sub> IU/mL increase in HBV DNA (aHR, 1.18 [1.05-1.34]). HBV suppression <200 IU/mL with HBV-active ART for ≥1 year significantly reduced the risk of HCC (aHR, 0.42 [0.24-0.73]).

**Conclusion:**

HIV/HBV-coinfected individuals on ART with detectable HBV DNA >200 IU/mL remained at increased risk for HCC. Heavy alcohol use and hepatitis C coinfection were prevalent in our cohort and also important determinants of HCC. To gain maximal benefit from ART for HCC prevention, sustained HBV suppression may be necessary.

Table. Risk of incident hepatocellular carcinoma associated with different categories of time-updated hepatitis B virus (HBV) DNA among HIV/HBV-coinfected persons who had quantitative HBV DNA measured prior to follow-up in the North American AIDS Cohort Collaboration on Research and Design (1995-2016; n=3,054; 30 incident hepatocellular carcinoma events identified).

| Characteristic                                     | No. Exposed | No. Events | Person-Time (95% CI) | Incidence Rate (95% CI) Events/1,000 Person-Years | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) |
|--|-------------|------------|----------------------|---|------------------------|-----------------------|
| <b>Time-updated HBV DNA, 200 IU/mL cut-off</b>     |             |            |                      |   |                        |                       |
| ≤200 IU/mL   | 2,355       | 17         | 15,844.9             | 1.1 (0.6-1.7)                                     | Reference              | Reference             |
| >200 IU/mL   | 1,488       | 13         | 5,031.4              | 2.6 (1.4-4.4)                                     | 2.60 (1.25-5.41)       | 2.70 (1.23-5.93)      |
| <b>Time-updated HBV DNA, 2,000 IU/mL cut-off</b>   |             |            |                      |   |                        |                       |
| ≤200 IU/mL   | 2,355       | 17         | 15,844.9             | 1.1 (0.6-1.7)                                     | Reference              | Reference             |
| 201-2,000 IU/mL                                    | 596         | 2          | 973.1                | 2.1 (0.45-9.17)                                   | 2.11 (0.45-9.59)       | 2.20 (0.50-9.59)      |
| >2,000 IU/mL                                       | 1,232       | 11         | 4,058.3              | 2.7 (1.4-4.8)                                     | 2.72 (1.26-5.86)       | 2.85 (1.24-6.57)      |
| <b>Time-updated HBV DNA, 200,000 IU/mL cut-off</b> |             |            |                      |   |                        |                       |
| ≤200 IU/mL   | 2,355       | 17         | 15,844.9             | 1.1 (0.6-1.7)                                     | Reference              | Reference             |
| 201-200,000 IU/mL                                  | 1,122       | 5          | 2,824.0              | 1.7 (0.6-4.0)                                     | 1.71 (0.63-4.87)       | 1.77 (0.63-4.94)      |
| >200,000 IU/mL                                     | 774         | 8          | 2,107.4              | 3.8 (1.6-7.5)                                     | 3.87 (1.66-9.06)       | 4.34 (1.72-10.94)     |

Abbreviations: CI=confidence interval; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HR=hazard ratio; RNA=ribonucleic acid  
\*Hazard ratios adjusted for age and calendar year at start of follow-up.

**136 HEPATOCELLULAR CARCINOMA AND HBV VIREMIA IN HIV/HBV-COINFECTED PERSONS IN NA-ACCORD**

H. Nina Kim<sup>1</sup>, Craig W. Newcomb<sup>2</sup>, Dena M. Carbonari<sup>2</sup>, Edward R. Cachay<sup>3</sup>, M John Gill<sup>4</sup>, Mark Hull<sup>5</sup>, Jay R. Kostman<sup>6</sup>, Joseph K. Lim<sup>7</sup>, Michael J. Silverberg<sup>8</sup>, Michael A. Horberg<sup>9</sup>, Angel Mayor<sup>10</sup>, Mari M. Kitahata<sup>1</sup>, Marina B. Klein<sup>11</sup>, Vincent Lo Re<sup>2</sup>, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>University of California San Diego, San Diego, CA, USA, <sup>4</sup>University of Calgary, Calgary, Canada, <sup>5</sup>University of British Columbia, Vancouver, Canada, <sup>6</sup>Philadelphia FIGHT, Philadelphia, PA, USA, <sup>7</sup>Yale University, New Haven, CT, USA, <sup>8</sup>Kaiser Permanente, Oakland, CA, USA, <sup>9</sup>Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, <sup>10</sup>Universidad Central del Caribe, Bayamon, Puerto Rico, <sup>11</sup>McGill University, Montreal, Canada

**Background:**

Chronic hepatitis B (HBV) is the predominant cause of hepatocellular carcinoma (HCC) worldwide. Although HBV coinfection is common in HIV, the determinants of HCC in HIV/HBV coinfection are poorly characterized. We examined the incidence and predictors of HCC in a multi-cohort study of HIV/HBV-coinfected individuals.

**Methods:**

We examined all HIV/HBV-coinfected persons (defined by positive HBV surface antigen, e antigen, or HBV DNA) within 22 cohorts of the North American AIDS Cohort Collaboration on Research and Design from 1995-2016. The main outcome, first occurrence of HCC, was verified by medical record review and/

**137 UPRISING CIRCULATION OF HBV-COMPLEX PROFILES WITH HBSAG VACCINE-ESCAPE MUTATIONS**

Lorenzo Piermatteo<sup>1</sup>, Mohammad Alkhatib<sup>1</sup>, Ada Bertoli<sup>1</sup>, Lavinia Fabeni<sup>2</sup>, Miriam Lichtner<sup>3</sup>, Massimo Marignani<sup>4</sup>, Caterina Pasquazzi<sup>4</sup>, Nerio Iapadre<sup>5</sup>, Giustino Parruti<sup>6</sup>, Giuseppina Cappiello<sup>7</sup>, Massimo Andreoni<sup>8</sup>, Loredana Sarmati<sup>8</sup>, Francesca Ceccherini-Silberstein<sup>1</sup>, Valentina Svicher<sup>1</sup>, Romina Salpini<sup>1</sup>

<sup>1</sup>University of Rome Tor Vergata, Rome, Italy, <sup>2</sup>IRCCS Lazzaro Spallanzani, Rome, Italy, <sup>3</sup>Sapienza University of Rome, Rome, Italy, <sup>4</sup>Andrea Hospital, Rome, Italy, <sup>5</sup>San Salvatore Hospital, L'Aquila, Italy, <sup>6</sup>Pescara General Hospital, Pescara, Italy, <sup>7</sup>Sandro Pertini Hospital, Rome, Italy, <sup>8</sup>Hospital of Rome Tor Vergata, Rome, Italy

**Background:** Vaccine-escape mutations can alter HBsAg recognition by antibodies thus challenging vaccine efficacy, promoting immunosuppression-driven HBV-reactivation and impairing HBsAg detection by immunoassays. Limited information is available on the circulation of vaccine-escape mutations, single or in complex mutational profiles, over time and their impact on serological parameters in the setting of HBV genotype-D.

**Methods:** This study includes HBsAg sequences from 947 viremic HBV genotype-D infected patients (pts) collected from 2005 to 2019. 21 vaccine-escape mutations (T116N-P120E/S-T126A/I/N/S-Q129H/R-T131I/N-M133I/L-C139S-K141E-P142S-D144A/E-G145A/R-A159G by Lazarevic, 2014) are analyzed.

**Results:** Median (IQR) HBV-DNA and ALT are 3.5(2.6-5.0)logIU/mL and 39(26-73) U/L. 4.2% of pts is HBsAg-negative despite HBV-DNA positivity. Overall, 17.7% (168/947) of pts harbor >1 vaccine escape mutation with the highest prevalence in subgenotype-D3 (23% for D3 vs 13.6% for other subgenotypes, P<0.001). Among them, 17.3% (29/168) show complex profiles characterized by >2 vaccine-escape mutations. Notably, the proportion of pts with complex profiles of vaccine-escape mutations increased over time: from 0.4% (1/237) in

2005-2009 to 3.0% (12/396) in 2010-2014 and to 5.1% (16/314) in 2015-2019,  $P=0.007$ , suggesting an increased circulation of viral strains with enhanced capability to evade humoral responses. Moreover, the presence of complex profiles correlates with lower HBsAg levels: median (IQR) 40(0-2905)IU/mL for pts with complex mutational profile vs 1688(348-6090) without them ( $p=0.0007$ ). Focusing on HBsAg-negativity, the presence of complex profiles also correlates with HBsAg-negativity despite HBV-DNA positivity (34.8% with >2 vaccine-escape mutations vs 6.7% and 2.3% with a single or no vaccine-escape mutations are HBsAg-negative,  $p=0.007$  and  $<0.0001$ ). Of note, HBsAg-negativity is strongly associated with the presence of T126I/A in combination with >1 additional vaccine-escape mutation (50% with vs 3.3% without T126I/A-containing profiles were HBsAg-negative,  $p<0.0001$ ).

**Conclusion:** Complex profiles of vaccine-escape mutations are detected in a not negligible fraction of HBV genotype-D infected pts, and correlate with lower HBsAg quantification and HBsAg-negativity despite ongoing viral replication. These mutations should be considered for a proper clinical interpretation of HBsAg results and their circulation should be taken into account for the development of novel vaccine formulation.

### 138 PHYLOGENETIC ANALYSIS OF THE TIMING OF SARS-CoV-2 INTRODUCTIONS INTO WASHINGTON STATE

Diana M. Tordoff<sup>1</sup>, Alex Greninger<sup>1</sup>, Pavitra Roychoudhury<sup>1</sup>, Joshua T. Herbeck<sup>1</sup>  
<sup>1</sup>University of Washington, Seattle, WA, USA

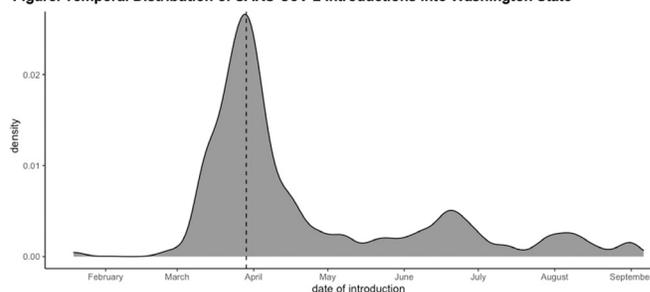
**Background:** The first confirmed case of SARS-CoV-2 in North America was identified in Washington state (WA) on January 21, 2020. By October 1, 2020, there were 89,974 confirmed cases of SARS-CoV-2 in WA. To understand the role of epidemic seeding events, we estimated the number and timing of introductions of SARS-CoV-2 lineages in WA using phylogenetic methods.

**Methods:** Our analysis used full genome SARS-CoV-2 sequences from GISAID sampled between December 2019 and September 2020. In order to incorporate phylogenetic uncertainty into our estimates, we generated 25 samples of sequences each with 5 random polytomy resolutions. Each sample contained 4918 high quality WA sequences and 6504 non-WA sequences, including 5056 non-WA sequences that were closest to WA sequences based on the raw number of mutations and a time-stratified random sample of 1448 additional non-WA sequences. Sequences were aligned using MAFFT and phylogenetic trees were reconstructed by lineage (GISAID clades S, L/V, G/GH and GR) using IQTREE. We then time-calibrated each phylogeny using the treeDate algorithm assuming a strict molecular clock and used maximum parsimony ancestral state reconstruction to estimate the state (WA or non-WA) of each node. Internal node date for the MRCA of each subclade of two or more sequences or the date of sampling for singletons was assumed to be the date of SARS-CoV-2 introduction.

**Results:** We estimated a median of 287 separate introductions (range 244-320) and 204 exported lineages (range 188-227) of SARS-CoV-2 into and out of WA through September 2020. Introductions began in mid-January 2020 and peaked in number on March 29, 2020 (Figure). Approximately 73% of introductions occurred prior to May 1, 2020. The majority of introductions were lineage G/GH (72%), followed by lineage GR (16%), S (5%) and L/V (7%). The resulting WA subclades ranged in size from 1-2193 sequences: 71% included just one sampled sequence, 9% included 2 WA sequences, 12% included 3-10 WA sequences, 4% included 11-50 sequences, and 4% were large subclades that included more than 50 WA sequences and were suggestive of extended local transmission chains.

**Conclusion:** We found phylogenetic evidence that the SARS-CoV-2 epidemic in WA was seeded by multiple ongoing introductions, although due to incomplete sampling our estimates underestimate the true number of introductions. In addition, lineages with the Spike 614G variant accounted for the majority (88%) of introductions.

Figure. Temporal Distribution of SARS-CoV-2 Introductions into Washington State



### 139 FROM TESTING TO MORTALITY: COVID-19 AND THE INVERSE CARE LAW IN SWITZERLAND

Julien Riou<sup>1</sup>, Radoslaw Panczak<sup>1</sup>, Christian Althaus<sup>1</sup>, Christoph Junker<sup>2</sup>, Damir Perisa<sup>2</sup>, Katrin Schneider<sup>2</sup>, Matthias Egger<sup>1</sup>

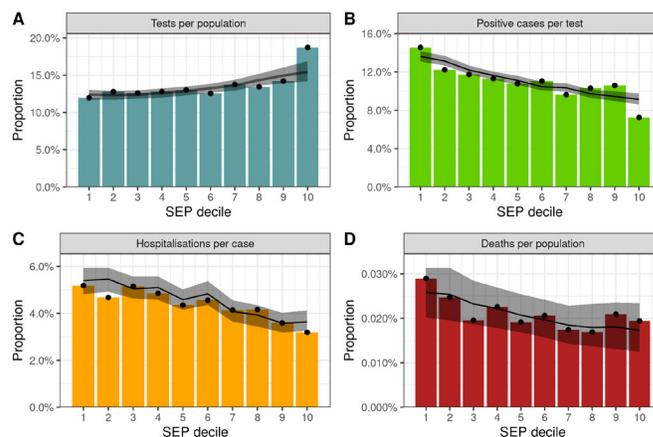
<sup>1</sup>University of Bern, Bern, Switzerland, <sup>2</sup>Federal Office of Public Health, Liebefeld, Switzerland

**Background:** The SARS-CoV-2 pandemic has created unprecedented challenges for society and healthcare systems worldwide. Switzerland is one of the more affected countries in Europe. We examined the association between socio-economic position (SEP) and SARS-CoV-2 tests, SARS-CoV-2-positive cases, COVID-19 hospitalisations and COVID-19 deaths in Switzerland.

**Methods:** We used surveillance data reported to the Federal Office of Public Health from March to October, 2020. We geocoded patients' residential addresses to determine the Swiss neighbourhood index of SEP, based on education and occupation of household heads, rent per square meter, and crowding. We used negative binomial regression models adjusted for sex, age, canton of residence and wave of the epidemic (first, March to June; second, July to October) to investigate the association between deciles of the SEP index (1st=lowest, 10th=highest) and four outcomes. We used different denominators: the 2018 Swiss population for tests and deaths, the number of tests for positive cases, and the number of positive cases for hospitalisations.

**Results:** Analyses were based on 1,130,405 SARS-CoV-2 tests, 143,101 positive cases, 6,367 hospitalisations and 1,749 deaths up to 31 October 2020. Figure 1 shows the distribution across deciles of neighbourhood SEP of (A) tests per population, (B) positive cases per test, (C) hospitalisations per case and (D) deaths per population (the black lines and shaded areas show the corresponding model prediction adjusted for sex, age, canton of residence and wave of the epidemic -- median posterior and 95% credible interval). The adjusted change in proportion per 1 decile increase in neighbourhood SEP was +2.4% (95% credible interval: 1.0 to 3.9) for tests per population, -2.4% (-3.6 to -1.1) for positive cases per test, -4.6% (-5.9 to -3.3) for hospitalisations per case and -4.5% (-7.7 to -1.4) for deaths per population.

**Conclusion:** This nation-wide study provides a comprehensive analysis of the association between SEP and SARS-CoV-2 testing, reported infections, and COVID-19-related hospitalisations and deaths. People living in neighbourhoods with higher SEP are more likely to be tested, but less likely to test positive, to be hospitalised or to die, a manifestation of the inverse care law where availability of care varies inversely with the need for it.



**140 SEX/GENDER DIFFERENCES IN TESTING, PRESENTATION, AND OUTCOMES OF SARS-CoV-2 INFECTION**

**Eileen P. Scully<sup>1</sup>**, Grant Schumock<sup>2</sup>, Martina Fu<sup>2</sup>, Eili Klein<sup>1</sup>, Sabra L. Klein<sup>2</sup>, Karen Bandeen-Roche<sup>2</sup>, Brian Garibaldi<sup>1</sup>, Amita Gupta<sup>1</sup>, for The CROWN registry team  
<sup>1</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Males have increased rates of severe illness and mortality from SARS-CoV2 compared to females. It is unknown whether this is due to differential care seeking, health status, illness presentation, comorbidities, and/or treatment responses. Understanding factors associated with sex/gender-based differences in COVID-19 outcomes is important for optimal care and therapeutics.

**Methods:** SARS-CoV-2 test positivity and admission rates were assessed between March and October of 2020 in the Johns Hopkins Medicine (JHM) system of five hospitals. Detailed patient-level data were extracted for hospitalized patients from the JH-CROWN, a COVID-19 registry utilizing the Hopkins Precision Medicine Analytics Platform. Descriptive statistics were used to analyze differences between males and females.

**Results:** 57% of 213,175 tests were done in females with a similar positivity rate (8.2% F vs 8.9%M). Males were more frequently hospitalized (28%F vs 33%M). Of 2608 hospitalized, more males reported fever, whereas more females reported headache, loss of smell and vomiting (p<0.05). Females had more favorable presenting respiratory parameters with lower respiratory rates and higher SpO2:FiO2 ratios (p<0.001). There was a similar burden of comorbidities (Charlson score) but differences in specific comorbidities: obesity and asthma higher among females (p<0.001), heart disease (p=0.06), complicated hypertension (p<0.01), chronic kidney disease, smoking and alcohol use higher among males (p<0.001). Admission and peak lab values showed lower IL-6, ferritin, CRP, higher absolute lymphocyte count and lower neutrophil:lymphocyte ratio in females (p=0.001 for all), but no difference in D-dimer or ESR. Test of interaction between sex and age was significant for IL-6 and ferritin (F test, p<0.05). Males and females received medications against SARS-CoV-2 with similar frequency with exception of tocilizumab which was used more frequently in males. Males had a higher incidence of severe/death outcomes across all ages (28% vs 36%, p<0.001) and in particular among the 18-49 age group (11% v 25%, p<0.001).

**Conclusion:** Females were less frequently admitted to the hospital after a diagnosis with SARS-CoV-2 infection. Despite an excess of obesity, females had a lower severity of respiratory parameters and lower inflammatory markers on presentation and had a lower frequency of severe outcomes from SARS-CoV-2 infection. Sex and age interactions with severe disease highlight critical risk features unique to males and females.

**141 RACIAL DISPARITIES IN COVID-19 POSITIVITY AMONG PEOPLE LIVING WITH HIV IN THE US**

**Jessica Y. Islam<sup>1</sup>**, Vithal Madhira<sup>2</sup>, Jing Sun<sup>3</sup>, Amy L. Olex<sup>4</sup>, Gregory D. Kirk<sup>3</sup>, Nora Franceschini<sup>5</sup>, Rena Patel<sup>6</sup>

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>Palia Software, Reno, NV, <sup>3</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>4</sup>Virginia Commonwealth University, Richmond, VA, USA, <sup>5</sup>UNC Chapel Hill, Chapel Hill, NC, <sup>6</sup>University of Washington, Seattle, WA, USA

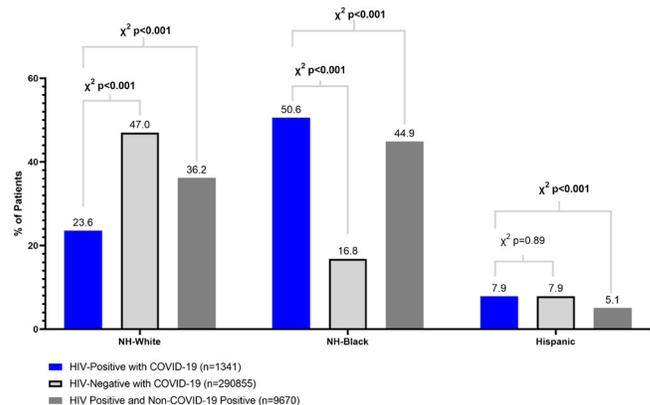
**Background:** Morbidity and mortality due to COVID-19 disproportionately impacts racial/ethnic minorities and adults with chronic diseases, potentially including people living with HIV (PLWH). Here, we present descriptive patient characteristics by COVID-19 positive and HIV status using the U.S. National COVID Cohort Collaborative (N3C).

**Methods:** Using N3C data, we conducted a retrospective cohort analysis of patients aged ≥ 18 years that had undergone COVID-19 testing. The N3C cohort includes patients with any encounter after 1/1/2020 with SARS-CoV-2 laboratory tests or diagnostic codes. Detailed electronic medical records are centrally gathered and data harmonized across health care organizations (34 sites). COVID-19 positivity was defined by a positive RT-PCR or antibody testing. HIV infection was defined based on standard diagnostic codes within 2 years prior to COVID-19 testing. Patient characteristics by COVID-19 positive and HIV status were compared using  $\chi^2$  tests.

**Results:** Over 2.1 million patients were captured in the N3C as of 11/25/2020, of whom 292,226 (13.6%) were COVID-19 positive; 11,011 (0.5%) were PLWH of whom 1341 (12.2%) tested COVID-19 positive. Compared to HIV-negative patients with COVID-19, COVID-19-positive PLWH were more likely to be 45+

years of age (62.3% vs.43.8%, p<0.001), male (70% vs. 46%, p<0.001), treated on an outpatient basis (9% vs. 5%, p<0.001), and have a modified Charlson comorbidity index score ≥3 (80% vs. 10%, p<0.001). Non-Hispanic (NH) Black COVID-19 positive adults were more likely to have HIV (51% vs. 17%, p<0.001), whereas NH-White were less likely (24% vs. 47%, p<0.001) (Figure 1). When comparing to PLWH without COVID-19, PLWH with COVID-19 were less likely to have a modified Charlson comorbidity index score of 3 or above (27% vs. 32%, p<0.001), with no significant differences in age or sex. COVID-19 positive PLWH were more likely to be NH-Black (51% vs. 45%, p<0.001) and Hispanic (8% vs. 5%, p<0.001), and, conversely, less likely to be NH-White (24% vs. 36%, p<0.001) when compared to PLWH without COVID-19 (Figure 1). **Conclusion:** Racial/ethnic minorities, including NH-Black and Hispanic adults, are disproportionately affected by COVID-19 pandemic, including PLWH. Our ongoing analyses will shed light on underlying mechanisms, such as types of comorbidities, that may lead to racial/ethnic disparities in the concurrence of HIV and COVID-19 positivity in the US.

Racial Differences by COVID-19 Positivity and HIV-Status in the United States National COVID Cohort Collaborative



**142 HIV AND COVID-19 INPATIENT OUTCOMES: A MATCHED RETROSPECTIVE MULTICENTRE ANALYSIS**

**Ming J. Lee<sup>1</sup>**, Colette Smith<sup>2</sup>, Sarah Fidler<sup>3</sup>, Lynsey C. Goodwin<sup>4</sup>, Lisa Hamzah<sup>5</sup>, Sarah Lawrence<sup>6</sup>, Rebecca Marchant<sup>7</sup>, Adrian Palfreeman<sup>8</sup>, Manish Pareek<sup>6</sup>, Kyle Ring<sup>7</sup>, Luke Snell<sup>8</sup>, John Thornhill<sup>9</sup>, Marie Williamson<sup>9</sup>, Achyuta Nori<sup>1</sup>, for RECEDE-C19 STUDY GROUP

<sup>1</sup>Guy's and St Thomas' NHS Foundation Trust, London, UK, <sup>2</sup>University College London, London, UK, <sup>3</sup>Imperial College London, London, UK, <sup>4</sup>The Pennine Acute Hospitals NHS Trust, Manchester, UK, <sup>5</sup>St George's University Hospital NHS Foundation Trust, London, UK, <sup>6</sup>University Hospitals of Leicester NHS Trust, Leicester, UK, <sup>7</sup>Imperial College Healthcare NHS Trust, London, UK, <sup>8</sup>King's College London, London, UK, <sup>9</sup>Barts Health NHS Trust, London, UK

**Background:**

Clinical outcomes for people living with HIV (PLWH) hospitalized with COVID-19 infections have shown mixed outcomes. We conducted a multicentre, UK retrospective matched cohorts' analysis.

**Methods:**

Index cases were HIV+ COVID-19 PCR+ patients hospitalized between dates 1st February - 31st May 2020. HIV-negative patients were matched to PLWH up to a 3:1 ratio across 6 sites in England, by hospital site, test date +/- 7 days, age +/- 5 years, gender, index of multiple deprivation decile (IMDD) +/- 1. The primary outcome was patients achieving ≥2-point improvement on a 7-point ordinal scale or discharge from hospital by day 28, whichever was earlier. Follow up was right-censored at day 28 for patients still in hospital. Baseline characteristics and outcomes were analysed by Cox-proportional hazards regression stratified by matching clusters using multiple imputation for missing data. The model adjusted for ethnicity, clinical frailty score, body mass index, baseline hypoxia, duration of symptoms, hypertension, diabetes, malignancy, cardiac, lung and renal disease.

**Results:**

68 PLWH and 181 HIV-negative patients were included. PLWH had an HR of 0.57 (95%CI 0.39, 0.85; p=0.005) of achieving 2-point improvement or discharge compared to HIV-negative patients. The effect size of HIV-status was attenuated (aHR 0.70; 0.43, 1.17; P=0.18) after adjustment in the multivariable

model (Table 1), with baseline frailty (aHR=0.79; 95%CI 0.65, 0.95; p=0.011), malignancy (aHR=0.37; 95%CI 0.17, 0.82; p=0.014) having a greater impact on the primary outcome. Proportion of deaths (19.1% vs 19.3%, p=0.266) and patients requiring ventilation (23.5% vs 17.1%, p=0.25) were similar between PLWH and HIV-negative patients. Sensitivity analyses adjusting for age and excluding missing data, remained consistent with main findings. PLWH were frailer (median clinical frailty score 3 vs 2, p=0.0069), and had higher proportion of malignancies (14.7% vs 9.9%, p=0.29) although not statistically significant. Number of non-HIV co-morbidities (2 vs 2, p=0.16) and median BMI (27.7 vs 29.4, p=0.19) were similar. The median CD4 count of PLWH was 352cells/μL (IQR 235, 619), and 63/68 (92.3%) were taking antiretroviral therapy.

#### Conclusion:

Although PLWH were less likely to achieve improvement or discharge, after adjustment the effect of HIV-status was attenuated. Increased baseline frailty and active malignancies remain associated with poorer COVID-19 outcomes.

increase in both IT and HIV case finding through IT, in COVID as compared to the pre-COVID period. Across all countries, total IT increased by 13% and HIV case finding through IT increased by 17% when comparing the COVID to the pre-COVID period. The number of HIV-positive people linked to treatment decreased in seven (64%) countries during the COVID period compared to pre-COVID. Across all countries, an increase of 3% in those HIV-positive people linked to treatment.

#### Conclusion:

While testing through PITC decreased during the COVID period, testing and case finding through IT increased. The increase in IT may reflect the actions of healthcare facilities and providers to ensure that HIV-exposed individuals identified by an index case were still tested. Focusing on IT may help programs effectively identify HIV-positive people, even during a pandemic or other disturbance.

Table 1. HIV testing and treatment initiation among adults (15+ years) in 11 countries, January-June 2019 and January-June 2020

|   |                  | Univariable |            |         | Multivariable |            |         |
|---|------------------|-------------|------------|---------|---------------|------------|---------|
|   |                  | HR          | 95% CI     | p-value | HR            | 95% CI     | p-value |
| <b>Primary outcome analysis – Factors associated with time to clinical improvement or discharge</b> |                  |             |            |         |               |            |         |
| HIV status  | Positive         | 0.57        | 0.39, 0.85 | 0.005   | 0.70          | 0.43, 1.17 | 0.18    |
| Ethnicity   | BAME             | 0.59        | 0.39, 0.89 | 0.012   | 0.86          | 0.52, 1.42 | 0.55    |
| Clinical frailty score  | Per 1 higher     | 0.74        | 0.63, 0.86 | <0.0001 | 0.79          | 0.65, 0.95 | 0.011   |
| Body Mass Index (kg/m <sup>2</sup> )  | <25              | 0.49        | 0.26, 0.96 | 0.12    | 0.46          | 0.21, 0.99 | 0.047   |
|   | 25-30            | 1.00        | -          | -       | 1.00          | -          | -       |
|   | 30-35            | 0.96        | 0.49, 1.90 | 0.99    | 0.99          | 0.47, 2.11 | 0.98    |
|   | 35+              | 0.65        | 0.32, 1.32 | 0.65    | 0.65          | 0.29, 1.48 | 0.30    |
| Hypoxic at admission  | Yes              | 0.60        | 0.54, 1.18 | 0.27    | 0.67          | 0.41, 1.09 | 0.10    |
| Days with symptoms at admission   | Per 1 day longer | 1.02        | 0.98, 1.06 | 0.28    | 1.00          | 0.95, 1.04 | 0.94    |
| Hypertension  | Yes              | 0.70        | 0.46, 1.06 | 0.094   | 0.88          | 0.52, 1.47 | 0.63    |
| Chronic cardiac disease   | Yes              | 0.49        | 0.24, 0.99 | 0.048   | 0.77          | 0.34, 1.74 | 0.53    |
| Chronic lung disease  | Yes              | 0.76        | 0.38, 1.55 | 0.45    | 1.08          | 0.48, 2.41 | 0.85    |
| Asthma  | Yes              | 1.37        | 0.75, 2.50 | 0.31    |               |            |         |
| Neurological  | Yes              | 1.17        | 0.62, 2.21 | 0.62    |               |            |         |
| Active malignancy   | Yes              | 0.38        | 0.19, 0.77 | 0.007   | 0.37          | 0.17, 0.82 | 0.014   |
| Diabetes  | Yes              | 0.79        | 0.50, 1.22 | 0.29    | 0.73          | 0.43, 1.25 | 0.26    |
| Rheumatological disease   | Yes              | 1.57        | 0.74, 3.33 | 0.24    |               |            |         |
| Chronic renal disease   | Yes              | 0.51        | 0.29, 0.90 | 0.019   | 0.79          | 0.40, 1.58 | 0.51    |

HR=hazard ratio; CI=confidence interval; BAME=Black, Asian and Minority Ethnicities. Results from Cox proportional hazards model stratified by matching clusters, with missing data accounted for using multiple imputation with chained equations (20 simulated datasets combined using Rubin's rules). Clinical centre, date of admission, gender, age and IMD decile were not included as co-variables as these were matching variables.

### 143 CHANGES IN HIV TESTING SERVICES AFTER COVID-19 IN 11 SUB-SAHARAN AFRICAN COUNTRIES

**Bakary Drammeh<sup>1</sup>, Anindya Dee<sup>1</sup>, Arielle Lasry<sup>1</sup>, Amy Medley<sup>1</sup>, Tiffany Aholou<sup>1</sup>, Randy Yee<sup>1</sup>, Helen Dale<sup>1</sup>, Sarah Porter<sup>2</sup>, Jonathan Mwangi<sup>3</sup>, Mahesh Swaminathan<sup>4</sup>, Ismelda Pietersen<sup>5</sup>, Veronica Muntanga<sup>6</sup>, Judith Shang<sup>7</sup>, Shirish Balachandra<sup>8</sup>, Stephenie Behel<sup>1</sup>**

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>Centers for Disease Control and Prevention, Pretoria, South Africa, <sup>3</sup>Centers for Disease Control and Prevention, Nairobi, Kenya, <sup>4</sup>Centers for Disease Control and Prevention, Abuja, Nigeria, <sup>5</sup>Centers for Disease Control and Prevention, Windhoek, Namibia, <sup>6</sup>Government of Zambia Ministry of Health, Lusaka, Zambia, <sup>7</sup>Centers for Disease Control and Prevention, Yaounde, Cameroon, <sup>8</sup>Centers for Disease Control and Prevention, Abidjan, Cote d'Ivoire

#### Background:

The COVID-19 pandemic has interrupted the implementation of many HIV prevention programs supported by the US President's Emergency Plan for AIDS Relief (PEPFAR), especially in sub-Saharan Africa. We evaluated the effects of COVID-19 pandemic (e.g., lockdowns, lack of personal protective equipment, community fears) on efforts to reach the UNAIDS 90-90-90 targets by HIV case finding using index testing (IT) and provider-initiated testing and counseling (PITC) as well as HIV treatment initiation.

#### Methods:

We conducted a descriptive analysis using programmatic data from persons aged 15 years and older reported to PEPFAR from 11 purposefully selected countries in sub-Saharan Africa. We calculated the percentage change in reported HIV case finding indicators during the COVID period, defined as January-June 2020, as compared to the pre-COVID period, during the same time frame in the preceding year, January-June 2019.

#### Results:

Of the 11 countries, persons tested for HIV through PITC declined in seven (64%) and persons testing positive declined in 10 (91%), comparing the COVID to pre-COVID periods (see Table 1). Across all countries, total HIV testing and total number of persons testing positive by PITC decreased by 20% and 23% when comparing the COVID to the pre-COVID period, respectively. In parallel, five of the 11 countries (Cameroon, DRC, Mozambique, Nigeria, South Africa) saw an

### 144 DRAMATIC DECLINE IN PUBLIC SECTOR HIV/STI TESTING DURING SARS-CoV-2 PANDEMIC, OREGON

**Timothy W. Menza<sup>1</sup>, Amy Zlot<sup>2</sup>, Jillian Garai<sup>2</sup>, Sarah Humphrey<sup>2</sup>, Josh Ferrer<sup>2</sup>**  
<sup>1</sup>Oregon Health & Science University, Portland, OR, USA, <sup>2</sup>Oregon Health Authority, Portland, OR, USA

**Background:** The SARS-CoV2 pandemic has dramatically affected public HIV and STI programs in the US. We determined the impact of SARS-CoV2 on public sector HIV and bacterial STI testing and diagnosis in Oregon.

**Methods:** We examined the periods of January through September of 2019 and 2020. We defined January through September 2019 and January through February 2020 as "before physical distancing," March 2020 through May 2020 as "the height of physical distancing" and June through September 2020 as "ongoing physical distancing." We used Poisson regression with robust standard errors to estimate incidence rate ratios and 95% confidence intervals (CI) comparing monthly HIV and bacterial STI testing and diagnosis rates during each phase of physical distancing.

**Results:** HIV and STI testing and diagnoses declined during physical distancing to nadirs in April and May 2020, with variable increases thereafter. Compared to before physical distancing, monthly HIV, NG/CT, and syphilis testing decreased both at the height of (by 50%, 58%, and 59%, respectively) and during ongoing physical distancing (by 28%, 44%, and 38%, respectively). Testing did not return to 2019 levels by September 2020. Monthly CT cases and early non-primary non-secondary and late/unknown duration syphilis cases were lower during both phases of physical distancing compared to before physical distancing. NG cases decreased 23% (95%CI: 2-40%) at the height of physical distancing but were comparable before physical distancing and during ongoing physical distancing. Compared to before physical distancing, HIV cases were 36% lower at the height of physical distancing and 12% greater during ongoing physical distancing; neither difference was statistically significant. In contrast, primary and secondary syphilis cases were 45% (95%CI: 22-72%) greater during ongoing physical distancing.

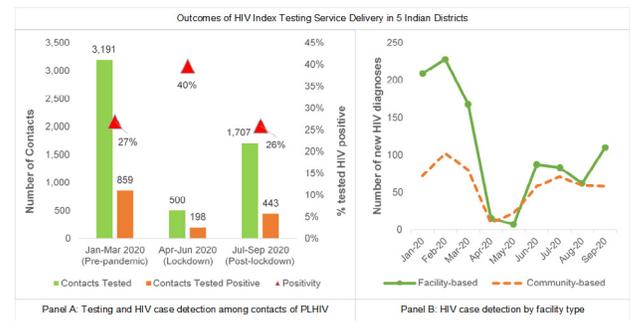
**Conclusion:** Public sector HIV and bacterial STI testing declined following implementation of physical distancing measures for SARS-CoV2 in Oregon. The large declines in testing likely reflect decreased access to/utilization of screening services during physical distancing, as cases of CT and early non-primary non-secondary and late/unknown duration syphilis, infections that are likely to present asymptotically, decreased significantly. Primary and secondary syphilis diagnoses increased, however, indicating ongoing sexual risk during physical distancing. Lack of timely diagnosis and treatment of HIV/STI during physical distancing may lead to increased transmission.

Table. HIV and bacterial STI testing before, at the height of, and during ongoing physical distancing, Oregon, January through September 2019 and 2020.

|  | Tests/cases per month (95% CI) |                               |                             | IRR (95% CI) <sup>1</sup> | P value <sup>2</sup> | P value <sup>3</sup> |
|--|--------------------------------|-------------------------------|-----------------------------|---------------------------|----------------------|----------------------|
|  | Before physical distancing     | Height of physical distancing | Ongoing physical distancing |                           |                      |                      |
| HIV tests  | 1063 (1018, 1109)              | 534 (295, 772)                | 769 (713, 825)              | 0.50 (0.32, 0.79)         | 0.72 (0.66, 0.79)    | <0.001               |
| HIV cases  | 15 (13, 18)                    | 10 (5, 15)                    | 18 (16, 19)                 | 0.64 (0.39, 1.07)         | 1.12 (0.92, 1.37)    | 0.088                |
| NG/CT NAAT   | 4915 (4747, 5082)              | 2073 (977, 3168)              | 2785 (2597, 2933)           | 0.42 (0.25, 0.72)         | 0.56 (0.52, 0.60)    | <0.001               |
| NG cases   | 512 (482, 542)                 | 394 (302, 496)                | 553 (502, 604)              | 0.77 (0.60, 0.98)         | 1.08 (0.97, 1.20)    | 0.033                |
| CT cases   | 1585 (1523, 1647)              | 1042 (754, 1330)              | 1353 (1278, 1429)           | 0.66 (0.50, 0.87)         | 0.85 (0.80, 0.91)    | 0.003                |
| Syphilis tests   | 1213 (1149, 1277)              | 500 (200, 800)                | 758 (699, 817)              | 0.41 (0.22, 0.75)         | 0.62 (0.57, 0.69)    | 0.004                |
| Primary & secondary syphilis cases                                       | 39 (34, 42)                    | 41 (31, 51)                   | 55 (48, 63)                 | 1.08 (0.83, 1.41)         | 1.45 (1.22, 1.72)    | 0.554                |
| Early non-primary non-secondary and late/unknown duration syphilis cases | 64 (59, 68)                    | 46 (22, 99)                   | 51 (45, 57)                 | 0.72 (0.53, 0.97)         | 0.80 (0.70, 0.92)    | 0.034                |

CI, confidence interval; CT, Chlamydia trachomatis; IRR, incidence rate ratio; NAAT, nucleic acid amplification test; NG, Neisseria gonorrhoeae; STI, sexually transmitted infection

<sup>1</sup>Compares height of physical distancing to before physical distancing  
<sup>2</sup>Compares ongoing physical distancing to before physical distancing  
<sup>3</sup>Includes IRR and syphilis



**145 COVID-19 IMPACT ON INDEX TESTING SERVICES IN 5 HIGH HIV PREVALENCE INDIAN DISTRICTS**

**Ajay K. Enugu<sup>1</sup>, Jalpa Thakkar<sup>1</sup>, Subash Ghosh<sup>2</sup>, Rose Pollard<sup>1</sup>, Allison M. McFall<sup>3</sup>, Ganjeevaram K. Vasudevan<sup>2</sup>, Easter Thamburaj<sup>2</sup>, Aditya Singh<sup>1</sup>, Shruti H. Mehta<sup>3</sup>, Sunil S. Solomon<sup>1</sup>**

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>YR Gaitonde Center for AIDS Research and Education, Chennai, India, <sup>3</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:**

Routine HIV testing for partners and children of PLHIV (e.g., index testing) is a key component of HIV prevention. Anecdotal information suggests that the COVID-19 pandemic's lockdowns and subsequent economic and mobility restrictions have impacted HIV testing programs; however, there is limited empirical data demonstrating this.

**Methods:**

Beginning in Oct 2019, we initiated index testing services in 5 high HIV prevalence districts in two Indian states (Maharashtra and Andhra Pradesh) at 55 sites (48 facility-based/7 community-based) to elicit and test contacts (spouses, sexual/needle-sharing partners, children) of known PLHIV. To assess the pandemic's impact on index testing outcomes among contacts, we compared outcomes in a pre-pandemic period (Jan-Mar 2020) to two post-pandemic periods: 1) a lockdown period (Apr-June 2020), and 2) a post-lockdown period when restrictions were eased (July-Sept 2020). Specifically, we compared the index testing cascade: number of contacts tested, number of contacts testing HIV+, proportion testing HIV+, and proportion initiating ART, by period and setting (facility vs. community-based).

**Results:**

In the pre-pandemic period, 3,191 contacts of 2,258 PLHIV were tested, among whom 859 tested HIV+ (27% positivity). By comparison, in the lockdown period, the number of contacts tested decreased by 84% (rate ratio [RR], 0.16; p<0.001) but positivity increased to 40%. Increases in the number tested were seen post-lockdown, but remained below pre-pandemic levels (RR, 0.54, p<0.001; Panel A). Overall, the pandemic's impact was more severe in facility vs. community sites (Panel B). By Sept 2020, the number of contacts testing positive returned to near pre-pandemic levels in community sites but remained <50% in facility sites. The proportion of newly diagnosed contacts who initiated treatment increased from 81% pre-pandemic to 88% in the lockdown and post-lockdown periods (p<0.01). The median time from diagnosis to ART initiation was 8 days pre-pandemic and during the lockdown, but reduced to 4 days post-lockdown.

**Conclusion:**

The pandemic resulted in significant declines in the testing of contacts of PLHIV and new HIV diagnoses, however linkage to ART among those newly diagnosed remained high. Our findings suggest that expansion of community-based service sites and/or incorporating strategies such as HIV self-testing may be needed to regain and maintain progress towards UNAIDS 95-95-95 goals, given the ongoing impacts of COVID-19.

**146 IMPACT OF VAGINAL STIs ON bNAb PROTECTION IN MACAQUES**

**David A. Garber<sup>1</sup>, Sundaram A. Vishwanathan<sup>1</sup>, Patricia Guenther<sup>1</sup>, Chunxia Zhao<sup>1</sup>, James Mitchell<sup>1</sup>, Shanon Ellis<sup>1</sup>, Marcos Manganare<sup>1</sup>, Michael Seaman<sup>2</sup>, Michel Nussenzeig<sup>3</sup>, Walid Heineine<sup>1</sup>, Janet McNicholl<sup>1</sup>**

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA, <sup>3</sup>The Rockefeller University, New York, NY, USA

**Background:**

Broadly neutralizing antibodies (bNAbs) confer durable protection in macaques against repeated mucosal SHIV challenges and are being evaluated clinically for pre-exposure prophylaxis (PrEP). In a prior study, bNAb 10-1074 provided durable protection against repeated vaginal SHIV challenge in macaques where the plasma concentration at breakthrough was 0.1µg ml<sup>-1</sup>. Sexually transmitted infections (STIs) increase mucosal HIV infection risk and have the potential to reduce PrEP efficacy. To evaluate the impact of STIs on bNAb efficacy we have developed a novel macaque vaginal STI model combining Treponema pallidum (TP), Chlamydia trachomatis (CT) and Trichomonas vaginalis (TV) and used it to reassess 10-1074 mediated protection against vaginal SHIV challenges.

**Methods:**

Six depot-medroxyprogesterone acetate (DMPA)-treated pigtail macaques were inoculated vaginally with TP (week -2, 4), CT (once every 3 weeks), and TV (once weekly) from week -2 through end of study. Macaques were passively immunized with 10-1074 (10 mg kg<sup>-1</sup>) once via subcutaneous injection (week -1). Beginning at week 0, animals were challenged vaginally with low-dose SHIVSF162P3, once weekly, until infection was confirmed via positive plasma viremia (LOQ=60 vRNA copies per ml). Three DMPA-treated controls that were similarly inoculated with STIs, but received no antibody, were challenged repeatedly with SHIV until infected. Among treated animals, longitudinal plasma samples were assayed via TZM-bl neutralization assay, using virions pseudotyped with 10-1074-sensitive HIV Env (X2088.c9), to determine 10-1074 concentrations.

**Results:**

STI-infected macaques that received 10-1074 were protected against a median of 12 SHIV challenges (range: 5-16), as compared to STI-infected untreated controls, which became infected following 2 challenges (P=0.0033, Log-rank test). Among macaques administered 10-1074, the median plasma bNAb concentration at the time of SHIV breakthrough was 1.0 µg ml<sup>-1</sup> (range:0.6-9.9 µg ml<sup>-1</sup>).

**Conclusion:**

A single subcutaneous administration of 10-1074 durably protected macaques against repeated vaginal SHIV challenges despite their being co-infected with ulcerative and nonulcerative vaginal STIs. However, higher bNAb levels may be required for protection against vaginal SHIV infection in the presence of STIs. This finding may impact dose selection for clinical development and highlights the importance of additional preclinical testing of efficacy in STI models.

## 147 PHASE 1 PK, SAFETY, AND ACCEPTABILITY STUDY OF 3-MONTH DAPIVIRINE VAGINAL RINGS

Albert Liu<sup>1</sup>, Clara Dominguez Islas<sup>2</sup>, Holly Gundacker<sup>3</sup>, Craig Hoesley<sup>4</sup>, Ariane Van der Straten<sup>5</sup>, Craig Hendrix<sup>6</sup>, May Beamer<sup>7</sup>, Cindy Jacobson<sup>8</sup>, Tara McClure<sup>9</sup>, Tanya Harrell<sup>10</sup>, Katherine Bunge<sup>9</sup>, John Steytler<sup>10</sup>, Jeremy Nuttall<sup>10</sup>, Jeanna Pfler<sup>11</sup>, Mark Marzinko<sup>6</sup>

<sup>1</sup>San Francisco Department of Public Health, San Francisco, CA, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>Statistical Center for HIV/AIDS Research and Prevention, Seattle, WA, USA, <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>5</sup>RTI International, Berkeley, CA, USA, <sup>6</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>7</sup>Magee–Womens Research Institute, Pittsburgh, PA, USA, <sup>8</sup>FHI 360, Durham, NC, USA, <sup>9</sup>Magee–Womens Hospital of UPMC, Pittsburgh, PA, USA, <sup>10</sup>International Partnership For Microbicides, Silver Spring, MD, USA, <sup>11</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA

**Background:** Vaginal rings (VRs) are a promising approach to long-acting HIV prevention. Extended duration VRs may reduce user burden and cost, streamline follow-up, and encourage adherence. We evaluated the safety, pharmacokinetics, adherence, and acceptability of two 3-month dapivirine (DPV) VRs compared with the monthly DPV VR.

**Methods:** MTN-036/IPM-047 enrolled 49 HIV-negative participants into a Phase 1, multi-site, randomized (1:1:1) trial comparing two extended duration (100 or 200 mg DPV) VRs used continuously for 13 weeks to a monthly 25 mg DPV VR. DPV concentrations were quantified in plasma, cervicovaginal fluid (CVF), and cervical tissue, at nominal timepoints. Geometric means ratios (GMRs) relative to the comparator ring were estimated using a fixed-effects model on log-transformed outcomes. Used rings were analyzed for residual DPV levels. Safety was assessed by adverse events (AEs), acceptability and adherence by self-report.

**Results:** Mean age was 30.0 (range 19–44) years; 41% were Black, 39% white, 8% Asian, and 12% of other race. Retention was 94% through day 91. There were no differences in the proportion of participants with grade  $\geq 2$  genitourinary AEs or grade  $\geq 3$  AEs in the extended duration vs. monthly VR arms ( $p=1.0$ ). Across timepoints, plasma and CVF DPV concentrations were higher in the 100 and 200 mg VR arms compared with the 25 mg arm (Table). Additionally, the peak concentration ( $C_{max}$ ) and Area Under the Concentration-Time Curve (AUC) for 0–28 days were 1.5 to 2 times higher for the extended duration VRs vs. monthly VR. Cervical tissue concentrations were consistently higher in the 200 mg VR (GMRs 2.36–3.97) and higher in the 100 mg VR at day 91 (GMR 3.04). A majority of participants (82%) reported being fully adherent, with no statistically significant differences between groups. Most participants reported liking the VRs (median (IQR): 8 (6–10) on 10-point Likert scale) and reported they were likely to use the VR if effective (median (IQR): 9 (7–10) on a 10-point Likert scale of future VR use). Based on manufacturer-reported DPV loads, the mean total DPV released over 13 weeks was estimated to be 11.2 mg for the 25 mg VR, 14.2 mg for the 100 mg VR, and 22.8 mg for the 200 mg VR.

**Conclusion:** The extended duration DPV VRs were well-tolerated and achieved higher DPV concentrations compared with the monthly DPV VR, likely translating into at least equal efficacy. These findings support further evaluation of 3-month DPV VRs for HIV prevention in women.

Table: Dapivirine Concentrations in Plasma (pg/ml), Cervicovaginal Fluid (ng/mg), and Cervical Tissue (ng/mg).

|   | Plasma          |                  |                   | CVF             |                  |                  | Cervical Tissue |                   |                   |
|---|-----------------|------------------|-------------------|-----------------|------------------|------------------|-----------------|-------------------|-------------------|
|   | 25 mg VR (n=16) | 100 mg VR (n=16) | 200 mg VR (n=16)  | 25 mg VR (n=16) | 100 mg VR (n=16) | 200 mg VR (n=16) | 25 mg VR (n=16) | 100 mg VR (n=16)  | 200 mg VR (n=16)  |
| <b>Day 28 Visit</b>   |                 |                  |                   |                 |                  |                  |                 |                   |                   |
| Geometric Mean, CV%   | 221, 30%        | 409, 25%         | 411, 38%          | 13, 88%         | 24, 92%          | 23, 129%         | 1.59, 143%      | 1.57, 1639%       | 3.76, 153%        |
| GMR (95% CI)  | --              | 1.85 (1.54–2.22) | 1.86 (1.48–2.32)  | --              | 1.90 (1.13–3.18) | 1.83 (1.01–3.29) | --              | 0.99 (0.29–3.37)  | 2.36 (1.13–4.93)  |
| <b>Day 56 Visit</b>   |                 |                  |                   |                 |                  |                  |                 |                   |                   |
| Geometric Mean, CV%   | 233, 35%        | 339, 31%         | 324, 127%*        | 8, 377%         | 24, 72%          | 21, 132%         |                 |                   |                   |
| GMR (95% CI)  | --              | 1.45 (1.16–1.81) | 1.41 (0.86–2.31)* | --              | 2.87 (1.21–6.85) | 2.60 (1.01–6.67) |                 |                   |                   |
| <b>Day 91 Visit</b>   |                 |                  |                   |                 |                  |                  |                 |                   |                   |
| Geometric Mean, CV%   | 220, 35%        | 276, 26%         | 315, 40%          | 11, 93%         | 14, 110%         | 17, 141%         | 0.70, 1065%     | 2.40, 336%        | 2.97, 176%        |
| GMR (95% CI)  | --              | 1.31 (1.05–1.64) | 1.45 (1.14–1.86)  | --              | 1.45 (0.75–2.79) | 1.74 (0.90–3.36) | --              | 3.04 (0.80–11.54) | 3.97 (1.15–13.76) |
| <b>AUC (0–28 days), pg/ml*days for Plasma, ng/mg*days for CVF</b> |                 |                  |                   |                 |                  |                  |                 |                   |                   |
| Geometric Mean, CV%   | 6222, 33%       | 11143, 29%       | 11567, 28%        | 411, 80%        | 796, 114%        | 806, 114%        |                 |                   |                   |
| GMR (95% CI)  | --              | 1.79 (1.45–2.21) | 1.86 (1.50–2.30)  | --              | 1.91 (1.04–3.50) | 1.96 (1.07–3.59) |                 |                   |                   |

## 148 INCIDENCE OF HIV INFECTION WITH DAILY OR ON-DEMAND ORAL PrEP WITH TDF/FTC IN FRANCE

Jean-Michel Molina<sup>1</sup>, Jade Ghosn<sup>1</sup>, Constance Delaugerre<sup>1</sup>, Gilles Pialoux<sup>1</sup>, Christine Katlama<sup>1</sup>, Laurence Slama<sup>1</sup>, Claire Pintado<sup>1</sup>, Michel Ohayon<sup>2</sup>, Hannane Mouhim<sup>3</sup>, Lambert Assoumou<sup>4</sup>, Bruno Spire<sup>5</sup>, Mohamed Ben Mechli<sup>6</sup>, Daniela Rojas Castro<sup>7</sup>, Dominique Costagliola<sup>8</sup>, for ANRS Prevenir study group

<sup>1</sup>Assistance Publique–Hôpitaux de Paris, Paris, France, <sup>2</sup>Center for Sexual Health, Paris, France, <sup>3</sup>Center for Sexual Health Checkpoint Paris, Paris, France, <sup>4</sup>Institut National de la Santé et de la Recherche Médicale, Paris, France, <sup>5</sup>Institut National de la Santé et de la Recherche Médicale, Marseille, France, <sup>6</sup>Agence nationale pour le Sida et les hépatites virales, Paris, France, <sup>7</sup>Coalition Plus, Pantin, France

**Background:** On-demand PrEP with TDF/FTC has been recommended as an alternative to daily PrEP for MSM by EACS, WHO and IAS-USA guidelines, but has not been endorsed yet by CDC due to limited real-world experience.

**Methods:** The ANRS Prevenir study is an ongoing prospective cohort study enrolling individuals at high risk for HIV infection on PrEP. MSM could opt for either daily or on-demand PrEP with TDF/FTC. At baseline, month 1 and every 3 months thereafter, subjects were tested for HIV using a 4th generation combined ELISA assay and other STIs and creatinine plasma levels were monitored. At each visit participants provided information regarding sexual behaviour, dosing regimen and drug adherence. Our main objective was to assess the overall HIV incidence in the study and per dosing regimen, as well as incidence of bacterial STIs (including syphilis, gonorrhoea, chlamydia and Mycoplasma genitalium) and viral hepatitis. Safety and study retention were also assessed. This analysis uses data accumulated up to September 30, 2020.

**Results:** From May 3rd 2017 to March 2nd 2019, 3067 subjects were enrolled across 22 sites in the Paris region, 44% being PrEP naive. Median age was 36 years (IQR: 29–43), 98.5% were MSM. At enrolment, PrEP was used daily and on demand by 50.5% and 49.5% of participants, respectively. Median number of partners in the last 3 months was 10 (5–20) and median number of condomless sex events in the prior 4 weeks was 2 (0–5). Median follow-up lasted 22 months and accumulated 5633 person-years (PY) with an overall HIV incidence in the cohort of 0.11 (95% CI: 0.04–0.23) per 100 PY. Six participants (3 daily, 3 on demand) acquired HIV-infection during the study period ( $P=0.99$ ). Condom use at last sexual intercourse was 19.6%. Overall STIs incidence was 73 (95% CI: 70.7–75.5) per 100 PY which remained stable during follow-up except during the COVID-19 lockdown when it dropped to 32.4 per 100 PY ( $P<10^{-4}$ ). HCV incidence was 0.69 per 100 PY. Incidence of participants lost to follow-up was 10.3/100 PY and 19 subjects (0.6%) discontinued PrEP for drug-related adverse events (gastrointestinal: 12, e-GFR  $< 70$  ml/mn: 4, other: 3).

**Conclusion:** In this PrEP cohort, enrolling mainly MSM at high risk of HIV-acquisition in Paris, HIV incidence was low whether participants used daily or on demand PrEP. There was a high incidence of bacterial STIs and HCV infection despite a drop in STIs incidence during the COVID-19 lockdown.

## 149 IMPACT OF COMMON SIDE EFFECTS ON PrEP PERSISTENCE DURING PREGNANCY IN SOUTH AFRICA

Dvora L. Joseph Davey<sup>1</sup>, Rufaro Mvududu<sup>1</sup>, Nyiko Mashele<sup>1</sup>, Maia Lesosky<sup>1</sup>, Linda-Gail Bekker<sup>2</sup>, Pamina M. Gorbach<sup>3</sup>, Thomas J. Coates<sup>3</sup>, Landon Myer<sup>1</sup>, for PrEP-PP Study Team

<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>Desmond Tutu HIV Foundation, Cape Town, South Africa, <sup>3</sup>University of California Los Angeles, Los Angeles, CA, USA

**Background:** Oral pre-exposure prophylaxis (PrEP) is a safe and effective prevention strategy to reduce women's risk of HIV in pregnancy and postpartum. Effective PrEP requires daily PrEP adherence, but little is known about how minor symptoms, which may be more common during pregnancy, overlap with PrEP side effects (SE) and could impact on PrEP persistence.

**Methods:** The PrEP in pregnancy and postpartum (PrEP-PP) study is an ongoing prospective cohort that enrolls consenting pregnant, HIV-uninfected women ( $>15$ -years) at first antenatal care (ANC) visit, followed through 12-months postpartum. Interviewers collected data on socio-demographics, SE, and PrEP use. We analyzed the reporting of SE and their association with PrEP persistence (defined as staying on PrEP at 3-months) and PrEP adherence (defined as taking PrEP  $>5$  of last 7 days at 3-month visit) with multivariable logistic regression adjusting for baseline maternal, gestational age and time in study.

**Results:** Between August 2019 and November 2020 we enrolled 759 pregnant women (median gestation=21 weeks; median age=26 years). Following PrEP counseling, 91% of pregnant women initiated PrEP at their first antenatal visit ( $n=690$ ), including 21 women  $<18$  years old (84%); 20% were married. Overall

73% of women on PrEP returned for a repeat prescription at 1-month, and 62% returned at 3-months. Among those returning at 3-months, 85% reported adhering to PrEP. Adherence was poorer with women who came in later in their pregnancy (>20 weeks) for their first ANC visit, or had lower education (completed primary vs. secondary school) ( $p < 0.05$ ). Over 31% of women on PrEP reported side effects at 1-month, mostly nausea/vomiting (22%), dizziness (25%), and headache (8%). Women on PrEP in the 1st or 2nd trimester had highest odds of reporting side effects (aOR=2.61; 95%CI=1.17, 5.84) compared to postpartum women adjusting for age, gestation and time in study. Women who reported SE at 1m had lower persistence and adherence at 3m compared to women who did not report SE (aOR=0.50; 95% CI=0.31, 0.81) adjusting for age, gestational age, and time in study (Table 1).

**Conclusion:** PrEP initiation was high in antenatal care in this setting but reporting of side effects that may be overlap with pregnancy symptoms was associated with poor PrEP persistence and adherence. This presents an opportunity for improved clinical management and counseling during pregnancy of nausea/vomiting to normalize early, transient side effects to improve PrEP adherence in pregnant women.

|  | Odds ratio (95% CI) | Adjusted odds ratio (95% CI)* |
|--|---------------------|-------------------------------|
| Gestational age (>20 weeks at first ANC visit) | 0.56 (0.36, 0.89)   | 0.57 (0.36, 0.93)             |
| Education (primary vs. secondary or higher)    | 0.60 (0.38, 0.93)   | 0.51 (0.32, 0.83)             |
| Reported side effects on PrEP                  | 0.56 (0.39, 0.91)   | 0.50 (0.31, 0.81)             |

\*Adjusted for age, gestational age and follow-up time

**150 COST-EFFECTIVENESS OF LONG-ACTING PrEP AMONG MSM/TGW IN THE US**

**Anne M. Neilan**<sup>1</sup>, Raphael J. Landovitz<sup>2</sup>, Mylinh H. Le<sup>1</sup>, Beatriz Grinsztejn<sup>3</sup>, Kenneth Freedberg<sup>1</sup>, Marybeth McCauley<sup>4</sup>, Nattanicha Wattananimitgul<sup>1</sup>, Myron S. Cohen<sup>5</sup>, Andrea Ciaranello<sup>1</sup>, David Paltiel<sup>6</sup>, Rochelle P. Walensky<sup>1</sup>

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>3</sup>Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil, <sup>4</sup>FHI 360, Washington, DC, USA, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>Yale School of Public Health, New Haven, CT, USA

**Background:**

HIV Prevention Trials Network (HPTN) 083 demonstrated superior efficacy of long-acting injectable cabotegravir (CAB-LA) compared to oral tenofovir disoproxil fumarate/emtricitabine (F/TDF) for HIV pre-exposure prophylaxis (PrEP). CAB-LA cost may be higher than that of generic F/TDF. We projected the clinical benefit of CAB-LA vs. F/TDF and estimated the cost at which CAB-LA would be cost-effective.

**Methods:**

Using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) simulation model, we examined 2 strategies: generic F/TDF (or branded F/TAF) and CAB-LA among high-risk men who have sex with men and transgender women (MSM/TGW, i.e. trial-eligible) starting PrEP in the US ( $n \sim 476,300$ ). We used trial and published data including: HIV incidence (off PrEP: 5.32/100PY; F/TDF (and F/TAF): 1.33/100PY; CAB-LA: 0.26/100PY); HIV transmissions off-PrEP attributable to high-risk MSM/TGW: 17,800/year (yr); 62% 6yr-PrEP retention. We assumed constant incidence and annual transmissions. Annual costs were: generic F/TDF \$8,400 (branded F/TAF \$16,900); CAB-LA \$28,000, and ART: \$24,500-\$39,600. Projected outcomes included HIV transmissions averted, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs, \$/QALY) over 10 yrs. We used a willingness-to-pay threshold of \$100,000/QALY. In sensitivity analysis, we varied PrEP costs and transmissions/yr. We also examined providing CAB-LA to all PrEP-eligible MSM/TGW ( $n \sim 1,905,300$ ) – not just those at high risk – with HIV incidence off PrEP: 1.54/100PY and HIV transmissions: 19,700/yr.

**Results:**

In the base case, compared to generic F/TDF (or branded F/TAF), CAB-LA increased life expectancy by 37,000 QALYs (37,000 QALYs) and costs by \$36.78B (\$20.14B), leading to an ICER of \$994,000/QALY (\$544,000/QALY, Table). CAB-LA would be cost-effective compared to F/TDF or F/TAF over 10yrs at a maximum price premium over F/TDF (F/TAF) of \$700/yr (\$1,800/yr). When offered to all PrEP-eligible MSM/TGW, CAB-LA would be cost-effective over 10yrs at a maximum price premium of \$200/yr (vs. F/TDF) or \$500/yr (vs. F/TAF).

**Conclusion:**

The superiority of long-acting injectable PrEP notwithstanding, the presence of highly effective alternatives limits the additional price difference that payers should be willing to pay for CAB-LA.

**Table.** Model-projected clinical, cost and cost effectiveness outcomes of long-acting injectable cabotegravir (CAB-LA) for HIV pre-exposure prophylaxis (PrEP) compared to oral PrEP over a 10-year horizon

| Strategy                     | Transmissions | Incremental QALY | Incremental cost, billion USD | ICER, \$/QALY |
|------------------------------|---------------|------------------|-------------------------------|---------------|
| <i>High risk MSM</i>         |               |                  |                               |               |
| F/TDF                        | --            | --               | --                            | --            |
| CAB-LA                       | 8,000         | 37,000           | 36.78                         | 994,000       |
| <i>All PrEP-eligible MSM</i> |               |                  |                               |               |
| F/TDF                        | --            | --               | --                            | --            |
| CAB-LA                       | 9,000         | 40,000           | 140.87                        | 3,522,000     |
| <i>High risk MSM</i>         |               |                  |                               |               |
| F/TAF                        | --            | --               | --                            | --            |
| CAB-LA                       | 8,000         | 37,000           | 20.14                         | 544,000       |
| <i>All PrEP-eligible MSM</i> |               |                  |                               |               |
| F/TAF                        | --            | --               | --                            | --            |
| CAB-LA                       | 9,000         | 40,000           | 79.18                         | 1,980,000     |

HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; F/TDF, tenofovir disoproxil fumarate/emtricitabine; F/TAF, tenofovir alafenamide fumarate/emtricitabine; CAB-LA, long-acting injectable cabotegravir; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men.

Results are discounted at 3 percent per year and rounded to the nearest thousand. The ICER is the difference in cost divided by the difference in life expectancy for each strategy compared with the next less costly strategy.

**151 SOCIAL NETWORKS PREDICT PrEP UPTAKE IN SEARCH STUDY IN RURAL KENYA AND UGANDA**

**Catherine A. Koss**<sup>1</sup>, Joshua R. Nugent<sup>2</sup>, Lillian B. Brown<sup>1</sup>, James Ayieko<sup>3</sup>, Jane Kabami<sup>4</sup>, Mucunguzi Atukunda<sup>4</sup>, Edwin D. Charlebois<sup>1</sup>, Florence Mwangwa<sup>4</sup>, Gabriel Chamie<sup>1</sup>, Craig Cohen<sup>1</sup>, Elizabeth A. Bukusi<sup>3</sup>, Maya L. Petersen<sup>5</sup>, Moses R. Kamya<sup>6</sup>, Diane V. Havlir<sup>1</sup>, Laura B. Balzer<sup>2</sup>

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>University of Massachusetts Amherst, Amherst, MA, USA, <sup>3</sup>Kenya Medical Research Institute, Nairobi, Kenya, <sup>4</sup>Infectious Diseases Research Collaboration, Kampala, Uganda, <sup>5</sup>University of California Berkeley, Berkeley, CA, USA, <sup>6</sup>Makerere University College of Health Sciences, Kampala, Uganda

**Background:** Peer support may be important for increasing PrEP use. However, little is known about the influence of social networks (connections between and among individuals) on PrEP use in sub-Saharan Africa. We aimed to assess whether social network contacts predicted PrEP uptake in rural Kenya and Uganda after accounting for known predictors of PrEP initiation.

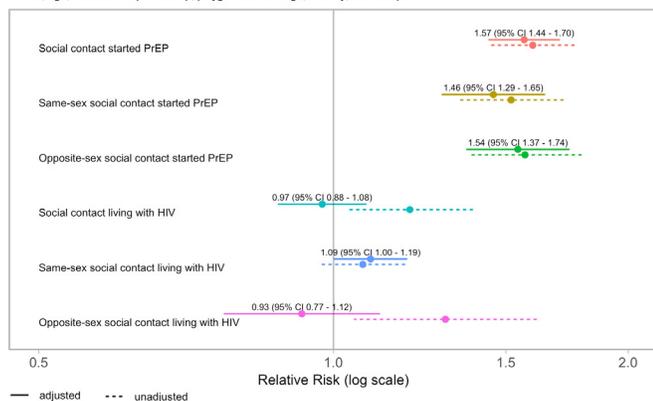
**Methods:** The SEARCH study (NCT01864603) offered TDF/FTC PrEP in 16 communities during population-level HIV testing starting in 2016-2017. Universal PrEP access with rapid or same-day start was offered to HIV-uninfected adults  $\geq 15$  years, with enhanced PrEP counseling for those at elevated HIV risk (based on serodifferent partnership, risk score, or self-identified risk). During population-level testing, persons were asked to name social contacts in 5 domains: health, money, emotional support, food, and free time. Named contacts were matched to community residents to build community-specific, sociocentric networks of 56,770 persons and 124,054 connections. Using targeted maximum likelihood estimation, we evaluated social network predictors of PrEP uptake within 1 year of population-level testing among persons at elevated HIV risk who had  $\geq 1$  matched first-degree contact, accounting for clustering by community and adjusting for sociodemographic factors (sex, age, serodifferent partner, polygamous marriage, mobility, occupation).

**Results:** Among 13,159 persons at elevated HIV risk, 8,898 (68%) had  $\geq 1$  matched network contact. Of the 8,898, 49% were women, 34% ages 15-24 years, 11% had a serodifferent partner, 14% had  $\geq 1$  contact who started PrEP, and 18% had  $\geq 1$  contact living with HIV (LHIV). Overall, 2,570/8,898 (29%) started PrEP. Persons with  $\geq 1$  contact who started PrEP were 57% more likely to start PrEP (adjusted risk ratio [aRR] 1.57, 95% CI 1.44-1.70,  $p < 0.001$ ) than those with contacts who did not start PrEP (Figure). Results were similar when stratified by sex and for same-sex and opposite-sex social contacts. Having an opposite-sex contact LHIV was associated with PrEP uptake in unadjusted analyses (RR 1.30, 95%CI 1.05-1.61,  $p = 0.009$ ), but not after adjustment for serodifferent partners and other factors (aRR 0.93, 95%CI 0.77-1.12,  $p = 0.39$ ).

**Conclusion:** Persons with a social contact who initiated PrEP were more likely to themselves start PrEP within 1 year of PrEP offer during population-level HIV testing. Interventions to facilitate peer support and strengthen social connections to other PrEP users should be considered to foster PrEP uptake.

## Social network predictors of PrEP uptake

Each type of network contact modeled separately; risk ratios (95% confidence intervals) estimated unadjusted and adjusted for sex, age, serodifferent partnership, polygamous marriage, mobility, and occupation



## 152 HSV-2 ACQUISITION IN A RANDOMIZED TRIAL OF CONTRACEPTIVE METHODS AMONG AFRICAN WOMEN

**Nelly R. Mugo<sup>1</sup>**, Renee Heffron<sup>2</sup>, Helen V. Rees<sup>3</sup>, Caitlin Scoville<sup>2</sup>, Charles Morrison<sup>4</sup>, Athena Kourtis<sup>5</sup>, Elizabeth A. Bukusi<sup>1</sup>, Mags Beksinka<sup>3</sup>, Neena M. Philip<sup>6</sup>, Ivana Beesham<sup>3</sup>, Jen Deese<sup>7</sup>, Vinodh Edward<sup>8</sup>, Deborah Donnell<sup>9</sup>, Jared Baeten<sup>10</sup>, for ECHO Trial Consortium

<sup>1</sup>Kenya Medical Research Institute, Nairobi, Kenya, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>University of the Witwatersrand, Johannesburg, South Africa, <sup>4</sup>FHI 360, Durham, NC, USA, <sup>5</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>6</sup>Columbia University, New York, NY, USA, <sup>7</sup>RTI Health Solutions, Research Triangle Park, NC, USA, <sup>8</sup>Aurum Institute, Johannesburg, South Africa, <sup>9</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>10</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Herpes simplex type 2 (HSV-2) infection causes recurrent genital ulcer disease and perinatal morbidity and is a strong risk factor for HIV acquisition. Women have higher HSV-2 prevalence than men, and conflicting data from observational studies suggest a possible association of HSV-2 acquisition with use of certain contraceptive methods, particularly intramuscular depot medroxyprogesterone acetate (DMPA-IM).

**Methods:** Within a randomized trial of the effect of three contraceptive methods – DMPA-IM, a copper intrauterine device (IUD), and a levonorgestrel (LNG) implant – on HIV acquisition, we assessed HSV-2 acquisition among women HSV-2 seronegative at baseline. Women who were HIV seronegative, aged 16–35 years, and seeking effective contraception were recruited from 12 sites in Kenya, the Kingdom of Eswatini, South Africa, and Zambia from 2015–2017. Follow-up was quarterly for 12–18 months, with HSV-2 serologic and confirmatory Western Blot testing done at enrollment and the final study visit according to a predetermined algorithm. Intention to treat analysis using Poisson regression with robust standard errors was done adjusting for age less than 25 years, having living children, living with a husband or primary partner, vaginal sex without a condom, having more than one sex partner, and having a new sex partner.

**Results:** Amongst 7829 HIV negative women randomized, 4062 (52%) were HSV-2 seronegative at baseline and 3898 had a conclusive HSV-2 result at the final visit. Of these, 614 (16%) acquired HSV-2 at an incidence of 12.4/100 person-years (p-y). HSV-2 incidence was 10.9/100 p-y among women assigned DMPA-IM, 13.7/100 p-y among those assigned the copper IUD, and 12.7/100 p-y among those assigned the LNG implant. Incidence rate ratios (IRR) for HSV-2 acquisition were 0.81 (95% confidence interval [CI] 0.67–0.99, p=0.04) for DMPA-IM compared with copper IUD, 0.86 (95% CI 0.71–1.05, p=0.15) for DMPA-IM compared with LNG implant, and 0.94 (95% CI: 0.78–1.13, p=0.50) for LNG implant compared with copper IUD. HSV-2 acquisition was associated with HIV seroconversion (IRR 3.6, 95% CI 2.9–4.6) during follow-up and detection of *Neisseria gonorrhoeae* (IRR 1.9, 95% CI 1.4–2.5) and *Chlamydia trachomatis* (IRR 1.4, 95% CI 1.2–1.7) infection at the final study visit.

**Conclusion:** HSV-2 incidence was high among this population of young African women and was not strongly associated with contraceptive method. HSV-2 incidence was lowest for DMPA-IM users.

153



## LABORATORY ANALYSIS OF HIV INFECTIONS IN HPTN 083: INJECTABLE CAB FOR PrEP

**Mark Marzink<sup>1</sup>**, Beatriz Grinsztejn<sup>2</sup>, Jessica Fogel<sup>1</sup>, Estelle M. Piwowar-Manning<sup>1</sup>, Brett Hanscom<sup>3</sup>, Lara Coelho<sup>2</sup>, Myron S. Cohen<sup>4</sup>, Alex R. Rinehart<sup>5</sup>, James F. Rooney<sup>6</sup>, Adeola Adeyeye<sup>7</sup>, Peter Anderson<sup>8</sup>, Marybeth McCauley<sup>9</sup>, Raphael J. Landovitz<sup>10</sup>, Susan Eshleman<sup>1</sup>, for the HPTN 083 Study Team

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, <sup>3</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>4</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>5</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>6</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>7</sup>National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, <sup>8</sup>University of Colorado, Aurora, CO, USA, <sup>9</sup>FHI 360, Washington, DC, USA, <sup>10</sup>University of California Los Angeles, Los Angeles, CA, USA

**Background:** HPTN 083 showed a 66% reduction in HIV incidence in cisgender men and transgender women who have sex with men (MSM/TGW) randomized to cabotegravir (CAB) 600 mg injections every 8 weeks (after an oral lead-in) vs. daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP). We originally reported 52 incident infections among 4566 participants (13 CAB, 39 TDF/FTC; annual incidence: 0.41% vs. 1.22%) with 5 additional baseline infections (2 CAB, 3 TDF/FTC). In post-hoc analysis, 1 incident infection in the CAB arm was later reclassified as a baseline infection; 1 additional baseline infection was also identified. We used virology and pharmacology assays to characterize these 58 cases (Table).

**Methods:** Concentrations of CAB and tenofovir (TFV) in plasma and TFV-diphosphate in dried blood spots were quantified by liquid chromatography-tandem mass spectrometry. HIV status and timing of HIV infection were assessed with an antigen/antibody (Ag/Ab) test, a discriminatory test, and RNA assays. Drug resistance testing was performed for samples with HIV RNA >500 copies/mL.

**Results:** Among 12 incident infections in the CAB arm: 5 had no recent CAB dosing; 3 occurred in the oral lead-in phase (1 had no CAB detected); 4 occurred despite on-time CAB injections and targeted CAB concentrations. Five of the 16 infections in the CAB arm had integrase resistance associated mutations (RAMs; Q148R or Q148K with accessory mutations, or R263K); 1 of these cases also had a non-nucleoside reverse transcriptase inhibitor (NNRTI) RAM. One case had NNRTI RAMs only and 1 had NNRTI RAMs with nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) RAMs. In the TDF/FTC arm, 37/39 incident infections occurred in participants with drug concentrations indicating sub-optimal or non-adherence. One infection was likely due to transmission of TDF/FTC-resistant HIV; 1 occurred despite targeted drug concentrations. Thirteen of the 42 infections in the TDF/FTC arm had RAMs: 3 had NRTI RAMs only; 3 had NRTI and NNRTI RAMs; and 7 had NNRTI RAMs only. Retrospective HIV RNA testing identified HIV infection earlier than Ag/Ab testing performed at study sites.

**Conclusion:** TDF/FTC and CAB are highly effective for HIV PrEP in MSM/TGW. Oral pill non-adherence likely contributed to higher HIV incidence among those randomized to TDF/FTC. Integrase inhibitor resistance was observed in some cases in the CAB arm. Long-acting CAB is an important addition to HIV prevention options.

| Study Arm           | CAB Arm | TDF/FTC Arm |
|---------------------|---------|-------------|
| Incident infections | 12      | 39          |
| Baseline infections | 4       | 3           |
| Total               | 16      | 42          |

## 154 INFECTED CELLS ARE CLONOTYPICALLY DIVERSE IN BLOOD &amp; LYMPH NODES SINCE FIEBIG STAGE I

**Pierre Gantner<sup>1</sup>**, Supraanee Buranapraditkun<sup>2</sup>, Marion Pardons<sup>3</sup>, Amélie Pagliuzza<sup>1</sup>, Rémi Fromentin<sup>1</sup>, Julie Mitchell<sup>4</sup>, Eugene Kroon<sup>5</sup>, Suteeraporn Pinyakorn<sup>6</sup>, Merlin Robb<sup>6</sup>, Nittaya Phanuphak<sup>7</sup>, Jintanat Ananworanich<sup>7</sup>, Denise C. Hsu<sup>6</sup>, Sandhya Vasan<sup>6</sup>, Lydie Trautmann<sup>8</sup>, Nicolas Chomont<sup>1</sup>

<sup>1</sup>Centre de Recherche du CHUM, Montreal, Canada, <sup>2</sup>Chulalongkorn University, Bangkok, Thailand, <sup>3</sup>Université de Montréal, Montreal, Canada, <sup>4</sup>Oregon Health and Sciences University, Portland, OR, USA, <sup>5</sup>SEARCH, Bangkok, Thailand, <sup>6</sup>US Military HIV Research Program, Bethesda, MD, USA, <sup>7</sup>Academic Medical Center, Amsterdam, Netherlands

**Background:** The initial cellular targets of HIV in lymphoid tissues remain unclear. Here, we used a single-cell approach to retrieve the phenotype, HIV envelope and T-cell receptor (TCR) sequences of HIV-infected cells in blood and lymph nodes from individuals at the earliest stage of HIV infection, prior to ART initiation.

**Methods:** Cross-sectional paired blood and lymph nodes samples from 21 acutely infected participants (n=3-5 individuals/Fiebig stage [I to V]) and 4 untreated chronically-infected controls enrolled in the RV254/RV304 studies (Bangkok, Thailand) were analyzed. The phenotype of productively infected (p24+) cells was analyzed by multiparameter flow-cytometry (HIV-Flow). Clonotype and viral characterization of single sorted infected cells was determined by TCR $\beta$  and Env (C2V5) sequencing, respectively.

**Results:** Productively infected p24+ cells were detected in blood and lymph nodes since the earliest stage of acute infection (Fiebig I) and their frequency increased with time. Phenotypic analysis of 12,067 p24+ cells from blood and lymph nodes showed that memory cells expressing CCR5, Ki67, ICOS, PD-1 and CXCR3 were preferentially infected at all stages. UMAP analysis revealed that infected cells were distributed in 11 cell clusters, and that their relative contribution to the overall pool of infected cells evolved rapidly across the different stages of acute infection and differed between blood and lymph nodes (Fig. 1). Although T follicular helper (Tfh) cells and particularly germinal center-Tfh were preferential HIV targets in lymph nodes during chronic infection, their contributions to the initial pool of infected cells were modest in acute infection. HIV-Env sequencing of 582 single-sorted p24+ cells showed a homogeneous population of HIV variants across blood and lymph nodes during all stages of acute infection, which diversified during chronic infection. In sharp contrast, distinct TCR $\beta$  were found in >99% of the cellular HIV targets (n=1,006 p24+ cells), indicating that initially infected cells were the product of independent infection events and that expansions in the pool of productively infected cells were rare early in infection.

**Conclusion:** HIV-infection is established by a limited number of HIV variants infecting a large pool of phenotypically and clonotypically distinct memory T cells in both blood and lymph nodes. The phenotype of infected cells differed between Fiebig stages, suggesting a rapid temporal evolution in HIV cellular targets during acute HIV infection.

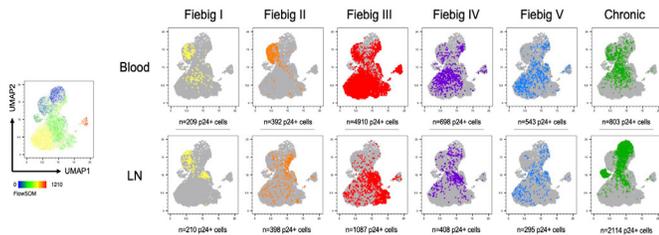


Fig 1. Cluster analysis of productively infected cells (p24+). Clustering and UMAP analyses were performed on extracted phenotyping data for all p24+ cells (n=12,067) from all participants and for both blood and lymph nodes. Cells clustered into 11 subsets (left panel). p24+ cells from a given Fiebig stage and a given compartment (blood or lymph node) are depicted as an overlay (color) on the total population of p24+ cells (grey) (right panels). The analysis reveals differences in the phenotypes of HIV-infected cells between blood and lymph nodes and between Fiebig stages.

**155 EVOLUTIONARY DYNAMICS OF HIV RESERVOIR CELLS VIA A NOVEL SINGLE-CELL MULTOMIC ASSAY**

**Kevin B. Einkauff<sup>1</sup>**, Matthew Osborn<sup>1</sup>, Ce Gao<sup>1</sup>, Elizabeth Parsons<sup>1</sup>, Chenyang Jiang<sup>1</sup>, Xiaodong Lian<sup>1</sup>, Xiaoming Sun<sup>1</sup>, Jane E. Blackmer<sup>1</sup>, Eric S. Rosenberg<sup>2</sup>, Xu Yu<sup>1</sup>, Mathias Lichterfeld<sup>3</sup>

<sup>1</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>2</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>3</sup>Brigham and Women's Hospital, Boston, MA, USA

**Background:** Latent reservoirs constitute a major barrier to HIV cure. Viral reservoir cell persistence may depend on proviral sequence, integration site and HIV transcription, but technical limitations have hindered efforts to obtain all three features from single infected cells. Here, we describe a novel technology that accomplishes this.

**Methods:** PBMC from 3 HIV+ patients, collected during pre-ART viremia and over 9+ years of continuous ART, were analyzed by a novel assay termed Parallel HIV RNA, Integration Site and Proviral Sequencing (PRIP-Seq). PBMC were diluted to single viral reservoir cells and subjected to parallel extraction of cellular DNA and RNA. Near-full-length proviral genomes and integration sites were obtained from DNA samples, and viral transcripts were detected by RT-ddPCR in corresponding RNA samples. Integration sites were annotated with genome-wide RNA-Seq, ATAC-Seq, ChIP-Seq, Hi-C and bisulfite sequencing data.

**Results:** Paired HIV RNA expression profiles and proviral sequences were determined for 872 individual proviruses. HIV RNA was detected in 45% and 35% of cells harboring genome-intact and defective proviruses, respectively. Integration sites were simultaneously obtained for 468 of these cells. Across

all patients and timepoints, proviruses in non-genic regions were less likely to express HIV RNA when compared to genic integrants (18% vs. 37%, p=0.003), and these non-genic regions were associated with multiple epigenetic features of repressive chromatin. Proviruses in satellite DNA produced no detectable RNA. Among proviruses in genes, HIV transcriptional silence correlated with increased upstream DNA methylation and reduced ATAC-Seq/activating ChIP-Seq reads in proviral 3D chromosomal contact regions. Longitudinal analysis suggested progressive enrichment of proviruses with reduced transcription and genomic/epigenetic integration site features of deeper latency during long-term ART, particularly among intact proviruses. However, several large proviral clones persisted for years despite ongoing HIV gene expression; these clones were located in close proximity to strong activating epigenetic chromatin marks.

**Conclusion:** Even after 9+ years of ART, a remarkable proportion of proviruses can be transcriptionally active, but these cells appear more vulnerable to immune-mediated clearance. Conversely, silent proviruses may have a survival advantage during long-term ART, seemingly due to distinct genomic/epigenetic features at integration sites and their 3D contact regions.

**156 NONINVASIVE PLASMA GLYCOMIC AND METABOLIC BIOMARKERS OF POSTTREATMENT HIV CONTROL**

**Leila B. Giron<sup>1</sup>**, Clovis S. Palmer<sup>2</sup>, Qin Liu<sup>1</sup>, Xiangfan Yin<sup>1</sup>, Emmanouil Pappasavvas<sup>1</sup>, Mohammad Damra<sup>1</sup>, Aaron R. Goldman<sup>1</sup>, Hsin-Yao Tang<sup>1</sup>, Rowena Johnston<sup>1</sup>, Karam Mounzer<sup>3</sup>, Alan Landay<sup>4</sup>, Luis J. Montaner<sup>1</sup>, Jeffrey Jacobson<sup>5</sup>, Jonathan Li<sup>6</sup>, Mohamed Abdel-Mohsen<sup>1</sup>

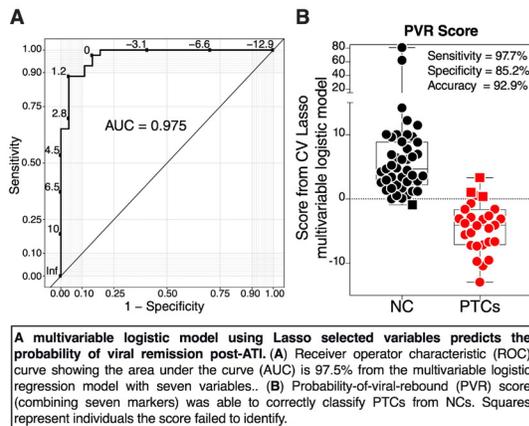
<sup>1</sup>Wistar Institute, Philadelphia, PA, USA, <sup>2</sup>Burnet Institute, Melbourne, Australia, <sup>3</sup>Philadelphia FIGHT, Philadelphia, PA, USA, <sup>4</sup>Rush University Medical Center, Chicago, IL, USA, <sup>5</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>6</sup>Brigham and Women's Hospital, Boston, MA, USA

**Background:** Non-invasive biomarkers that predict HIV remission after antiretroviral therapy (ART) interruption are urgently needed. Such biomarkers can improve the safety of analytic treatment interruption (ATI) and provide mechanistic insights into the pathways involved in post-ART HIV control.

**Methods:** We examined two ATI cohorts: 1) Philadelphia cohort: a cohort of 24 HIV+ ART-suppressed individuals; 2) ACTG cohort: 74 participants of six ATI studies, including 47 non-controllers (NCs) and 27 post-treatment controllers (PTCs), a rare population sustains virologic suppression after ART-cessation. Pre-ATI plasma metabolome was measured by mass spectrometry. Pre-ATI plasma and IgG glycomes were profiled using capillary electrophoresis and lectin microarray. The J-Lat and THP-1 cell lines were used to examine latent HIV reactivation and myeloid inflammation, respectively. Cox and Logistic regression models with or without adjusting for confounders (age, gender, ethnicity, ART initiation, ART duration, and pre-ATI CD4 count) were used for statistical analyses. False discovery rate (FDR) was calculated to account for multiple comparisons.

**Results:** We identified 13 plasma glycans and metabolites that their pre-ATI levels associate with either faster (n=5; mostly pro-inflammatory molecules) or delayed (n=8; mostly anti-inflammatory molecules) viral rebound post-ART in both discovery and validation cohorts (hazard ratios  $\geq 2$  or  $\leq 0.5$ ; FDR<10%; P<0.05 after adjusting for confounders mentioned above). The pre-ATI levels of 10 of these markers were significantly different between PTCs and NC (FDR<0.05). Among the top markers, pre-ATI levels of L-glutamic acid predicted delayed rebound (P=0.005) and were higher in PTCs compared to NCs (P=0.0096). In vitro, L-glutamic acid significantly inhibited PMA or  $\alpha$ CD3/ $\alpha$ CD28 mediated latent HIV transcription in the J-Lat HIV latency model (P<0.0001). L-glutamic acid also prevented THP-1 inflammation upon LPS stimulation (P<0.02). Finally, using the machine learning algorithm, lasso (least absolute shrinkage and selection operator), we combined this set of biomarkers into two multivariate models: Cox model that predicts time-to-viral-rebound with 74-76% capacity; and logistic model that predicts probability-of-viral-rebound (PVR score) with 97.5% capacity.

**Conclusion:** We fill a major gap in HIV cure research by identifying non-invasive biomarkers, with potential functional significance, that predict duration and probability of viral remission after treatment interruption.



### 157 PD-1 BLOCKADE ENHANCES THERAPEUTIC BENEFITS OF VACCINE IN A CHRONIC SIV/MACAQUE MODEL

**Sheikh A. Rahman**<sup>1</sup>, Bhruyu Yagnik<sup>1</sup>, Alexander P. Bally<sup>1</sup>, Kristen N. Morrow<sup>1</sup>, Wang Shelly<sup>1</sup>, Thomas H. Vanderford<sup>1</sup>, Gordon J. Freeman<sup>2</sup>, Rafi Ahmed<sup>3</sup>, Rama R. Amara<sup>1</sup>

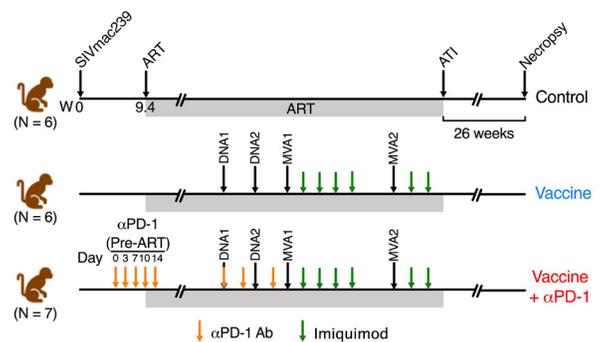
<sup>1</sup>Yerkes National Primate Research Center, Atlanta, GA, USA, <sup>2</sup>Harvard Medical School, Boston, MA, USA, <sup>3</sup>Emory Vaccine Center, Atlanta, GA, USA

**Background:** Limitations to achieving a complete HIV-1 infection cure include failure to remove latent reservoirs, CD8 T cell dysfunction due to immune exhaustion, and failure to induce anti-viral CD8+ T cells in lymphoid tissue where most reservoirs persist, even under anti-retroviral therapy (ART). These findings warrant the development of strategies that can simultaneously reduce reservoir burden under ART, improve virus-specific T cell functions, enhance cytolytic CD8 T cell localization to the lymphoid tissues, and sustain these responses in the absence of ART. The combined action may enable an effective viral control in the absence of ART potentially leading to complete remission.

**Methods:** Three groups of rhesus macaques (RMs) were infected with SIVmac239 intrarectally and ART was initiated at 10 weeks post infection. Two groups were subsequently immunized with two DNA-SIV239/MVA-SIV239 prime/boost vaccines. The third group served as the control group. Both vaccinated groups also received the ectopic application of imiquimod (a TLR7 agonist) as a potential immune adjuvant/latency reversal agent. The Vaccine and PD-1 group received anti-PD-1 antibody prior to ART initiation and concomitant with DNA priming. All vaccinations were carried out under complete viral suppression by ART. RMs were followed for 26 weeks post-analytical treatment interruption and tracked for the viral rebound, development of AIDS, and survival. Key parameters such as T cell response, reservoirs, and lymph node localization of cytolytic CD8 T cells were interrogated longitudinally at key time points of the study.

**Results:** We show that CD40L adjuvanted DNA/MVA vaccine induced highly functional SIV-specific CD4+ and CD8+ T cell responses in blood, gut, and lymph nodes (LN) under anti-retroviral therapy. Combining PD-1 blockade with vaccine markedly increased the frequency of granzyme B+ perforin+ CD8+ T cells in blood and LN, enhanced their localization to BCF, and reduced viral reservoir. Upon ART interruption, combination therapy showed marked preservation of the granzyme B+ CD8+ T cells in the T cell zone and BCF regions of LN, maintained high SIV antigen-recognition breadth, showed notable control of reemerging viremia, and significantly improved survival, but not vaccine alone or control animals.

**Conclusion:** Our findings reveal that PD-1 blockade enhances the therapeutic benefits of vaccination by improving and sustaining the function and localization of vaccine-induced CD8 T cells to BCF and decreasing viral reservoirs.



### 158 TYPE I INTERFERON-ASSOCIATED GENE EXPRESSION PREDICTS TIME TO VIRAL REBOUND ON TI

**Penny Zacharopoulou**<sup>1</sup>, Emanuele Marchi<sup>1</sup>, Ane Ogbe<sup>1</sup>, Nicola Robinson<sup>1</sup>, Helen Brown<sup>1</sup>, Mathew Jones<sup>1</sup>, Lucia Parolini<sup>1</sup>, Matthew Pace<sup>1</sup>, Nicholas Grayson<sup>1</sup>, Pontiano Kaleebu<sup>2</sup>, Helen V. Rees<sup>3</sup>, Sarah Fidler<sup>4</sup>, Goulder Philip<sup>1</sup>, Paul Klenerman<sup>1</sup>, John Frater<sup>1</sup>

<sup>1</sup>University of Oxford, Oxford, UK, <sup>2</sup>Uganda Virus Research Institute, Entebbe, Uganda, <sup>3</sup>Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, <sup>4</sup>Imperial College London, London, UK

**Background:** As there is currently no cure for HIV, achieving antiretroviral treatment (ART)-free viral suppression has been made the focus of scientific efforts. In the absence of biomarkers that predict time to viral rebound, the evaluation of new therapeutic strategies requires treatment interruption (TI), which may confer risk. All but a rare subpopulation of people living with HIV experience viral rebound shortly after TI. However, the drivers of this phenotype have not yet been determined. If remission is determined by aspects of host immunity this may be evident by studying gene expression.

**Methods:** To explore the molecular differences between early and late rebounders, we present a longitudinal analysis of the host transcriptome that explores key genetic signatures associated with time to HIV rebound. We sequenced expressed host mRNA from South African women enrolled in the SPARTAC clinical trial, and who received treatment for up to 48 weeks, starting in primary infection. We studied CD4+ T-cells sampled at treatment interruption (wk 48). We used DESeq2 to quantify and transform our data, Gene Set Enrichment Analysis (GSEA) with the Reactome database and Weighted Gene Correlation Network Analysis (WGCNA) to identify putative genetic signatures associated with clinical outcomes. Genes identified by WGCNA to be correlated with time to rebound were screened using Cox Regression with LASSO to determine a gene signature to predict time to viral rebound.

**Results:** GSEA showed an IFN-I response pathway enrichment in sustained controllers (SC) (>500 days to rebound) versus non-sustained controllers (non-SC) (<500 days to rebound). WGCNA identified three modules of genes associated with the SC phenotype and one of them was found to be associated with both SC phenotype and time to rebound, as a continuous variable. IFN-I response was found to be enriched in this module. Two of five genes that were found to be correlated with time to rebound, were selected to construct a signature of Risk Score, correlating with smaller likelihood of rebounding earlier. A Kaplan-Meier curve of gene expression-based Risk Score (RS), predicted the likelihood of early and late post-TI rebound.

**Conclusion:** IFN-I response gene signature is enhanced in people with HIV stopping ART who rebound >500 days. The expression of TRIM25 and ISG15 may predict time to rebound at the point of TI.

### 159 HIV-1 PROVIRUS CANNOT BE REACTIVATED IN PATIENTS ON TREATMENT WITH ART AND DASATINIB

**Lorena Vigón**<sup>1</sup>, Paula Martínez-Román<sup>1</sup>, Juan Ambrosioni<sup>2</sup>, Antonio Navarro<sup>3</sup>, Adam Spivak<sup>4</sup>, Miguel Cervero<sup>5</sup>, Jose M. Miro<sup>2</sup>, Paula Prieto<sup>3</sup>, Christoph Wyen<sup>6</sup>, Christian Hoffmann<sup>7</sup>, José Alcamí<sup>1</sup>, Verónica Briz<sup>1</sup>, Vicente Planelles<sup>4</sup>, María Rosa López-Huertas<sup>1</sup>, Mayte Coiras<sup>1</sup>

<sup>1</sup>Instituto de Salud Carlos III, Madrid, Spain, <sup>2</sup>Hospital Clinic of Barcelona, Barcelona, Spain, <sup>3</sup>Hospital Universitario de Bellvitge, Barcelona, Spain, <sup>4</sup>University of Utah, Salt Lake City, UT, USA, <sup>5</sup>Hospital Universitario Severo Ochoa, Madrid, Spain, <sup>6</sup>University Hospital of Cologne, Cologne, Germany, <sup>7</sup>ICH Study Center, Hamburg, Germany

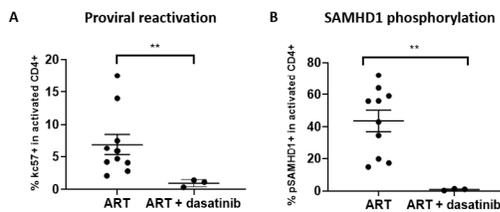
**Background:** CD4+ T cells from patients with chronic myeloid leukemia (CML) on treatment with dasatinib are resistant to HIV-1 infection ex vivo.

The main mechanism for this antiviral activity is the inhibition of SAMHD1 phosphorylation. In this study, we analyzed the reactivation of HIV-1 provirus from PBMCs of infected individuals with CML who were on treatment with ART+dasatinib.

**Methods:** Due to low estimated incidence of HIV+CML (1:65,000), only 6 HIV-infected male individuals with CML were recruited in Spain and Germany for this study. Three of these individuals had been on treatment with standard ART+dasatinib for median 1.6 yrs (IQR 1.5-5.3 yrs). CD4>500 in 2/3 patients (CD4/CD8 0.70±0.8). PBMCs from 14 HIV+ male patients with CD4>500 (CD4/CD8 0.95±0.3), undetectable viremia and similar standard ART were used as controls. Cell populations were analyzed by flow cytometry and plasma cytokines by Luminex. Proviral integration was quantified by dPCR. Proviral reactivation was analyzed in purified CD4 after activation with antiCD3/CD28 microbeads plus IL2 for 7 days and then PMA/ionomycin and brefeldin A for 24h. Cells were analyzed by flow cytometry after intracellular staining with anti-p24(kc57)-FITC and anti-pSAMHD1-PE.

**Results:** 1) Proviral integration was reduced 5.7-fold in HIV+ individuals on ART+dasatinib, in comparison with HIV+ individuals treated with ART. 2) Reactivation of provirus was reduced 4.6-fold ( $p<0.01$ ). 3) SAMHD1 phosphorylation was reduced 40-fold ( $p<0.01$ ). 3) Levels of homeostatic cytokine IL-7 were reduced 1.7-fold in plasma. 4) CD4 effector subpopulations TEM and TEMRA were reduced 1.6-fold.

**Conclusion:** Proviral reactivation in PBMCs from HIV+ individuals on treatment with ART+dasatinib was hindered in comparison with individuals only on ART. Several mechanisms may be involved: 1) The cytostatic effect of dasatinib that protected SAMHD1 from phosphorylation in response to activating stimuli; 2) The smaller reservoir size in individuals treated with ART+dasatinib, favoring TCM over TEM and TEMRA that are a major source for reservoir replenishment during ART; 3) The reduced plasma levels of IL-7 in the presence of dasatinib that may interfere with reservoir replenishment; 4) The amount of defective proviruses in ART+dasatinib treated individuals that should be determined. Dasatinib constitutes a novel and promising adjuvant therapy of ART to control reservoir size and reactivation in HIV chronically infected patients.



## 160 DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV8-MEDIATED GENE TRANSFER

Joseph P. Casazza<sup>1</sup>, Evan M. Cale<sup>1</sup>, Sandeep Narpala<sup>1</sup>, Laura Novik<sup>1</sup>, Galina V. Yamshchikov<sup>1</sup>, Bob C. Lin<sup>1</sup>, Janardan P. Pandey<sup>2</sup>, Adrian McDermott<sup>1</sup>, Mario R. Roederer<sup>1</sup>, Alejandro Balazs<sup>3</sup>, David Baltimore<sup>4</sup>, Richard A. Koup<sup>1</sup>, Julie E. Ledgerwood<sup>1</sup>, John R. Mascola<sup>1</sup>, for the VRC603 Team

<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>2</sup>Medical University of South Carolina, Charleston, SC, USA, <sup>3</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>4</sup>California Institute of Technology, Pasadena, CA, USA

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

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

**Results:** Product administration was well tolerated. No serious adverse events were attributed to product. Peak VRC07 concentrations were 0.17-0.43 µg/ml in the 5x1010 dose group, 0.23-0.74 µg/ml in the 5x1011 dose group and 1.1-1.2 µg/ml in the 2.5x1012 dose group. The data from 5 of the 8 volunteers suggest a pattern of antibody production defined by an early peak in VRC07 concentration followed by a decrease in concentration and then a slow secondary increase in concentration after 16 wks. In 4 of these 5 volunteers VRC07 concentration

either increased or remained stable for >1y. In the 3 volunteers who did not show a secondary increase in VRC07 production, anti-VRC07 antibodies (ADA) were detected. In each case anti-VRC07 antibodies bound both VRC07 and the VRC07 Fab fragment. No correlation between the subject heavy chain IgG1 allotype and presence of ADA was found. After protein A IgG purification, in vitro IgG containing VRC07 was characterized. Measured VRC07 closely correlated with neutralization activity. In the 7 individuals where IgG containing VRC07 was characterized, pseudovirus neutralization IC80s for 5 tier 2 pseudovirus were similar to reported IC80s for ex vivo produced VRC07. Neutralization of pseudovirus infections by purified IgG containing in vivo produced VRC07 was inhibited by the VRC07 paratope binding antibody 5C9.

**Conclusion:** AAV vectors can safely be used to stably produce biologically active HIV-1 specific bNAbs in humans for over 1-year. AAV8 mediated gene transfer offers a means of generating vectored immunoprophylaxis in humans but the reasons for the induced ADA responses need to be understood to optimize future gene transfer protocols.

161



## A PLACEBO-CONTROLLED ATI TRIAL OF HTI VACCINES IN EARLY TREATED HIV INFECTION

Lucía Bailón<sup>1</sup>, Anuska Llano<sup>2</sup>, Samandhy Cedeño<sup>2</sup>, Miriam B. Lopez<sup>1</sup>, Yovaninna Alarcon<sup>1</sup>, Pep Coll<sup>2</sup>, Àngel Rivero<sup>3</sup>, Anne R. Leselbaum<sup>4</sup>, Ian McGowan<sup>5</sup>, Devi SenGupta<sup>6</sup>, Bonaventura Clotet<sup>2</sup>, Christian Brander<sup>2</sup>, Jose Molto<sup>1</sup>, Beatriz Mothe<sup>2</sup>, for the AELIX-002 Trial Group

<sup>1</sup>Fundació Lluita Contra la Sida, Badalona, Spain, <sup>2</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>3</sup>Projecte dels NOMS-Hispanosida, BCN Checkpoint, Barcelona, Spain, <sup>4</sup>AELIX Therapeutics S.L., Barcelona, Spain, <sup>5</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>6</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** HTI is a novel HIV vaccine immunogen designed at redirecting cellular immune responses to HIV targets associated with viral control.

**Methods:** The AELIX-002 trial (NCT03204617) was a randomized, single-center, placebo-controlled trial to evaluate the safety, immunogenicity and antiviral effect of DNA.HTI (D), MVA.HTI (M) and ChAdOx1.HTI (C) vaccines after discontinuation of ART in early-treated people living with HIV (PLWH). 45 participants were randomized (2:1) to receive heterologous prime-boost vaccination regimens consisting of DDDMM followed by CCM, or matched placebo (P). During a 24-week analytical treatment interruption (ATI), plasma viral load (pVL) was monitored weekly and ART was resumed if pVL >100,000 copies/mL, or >10,000 copies/mL over 8 weeks, and/or CD4<350.

**Results:** A total of 45 participants received DDDMM (n=30) or PPPPP (n=15). Of the 45 participants, 41 further completed the CCM (n=26) or PPP (n=15) regimen and entered the ATI. Immunizations were well tolerated, with no SAEs, and were immunogenic in 97% of vaccine recipients (defined by a >2-fold increase in HTI-specific T cell responses compared to baseline). Median (range) increase in total frequencies of HTI-specific T cells from baseline was 1,499 (120 to 3,150) SFC/million PBMC. At time of ATI start, 71% (0 to 100) of the total anti-HIV-1 T-cell response was HTI-specific. For participants without any potentially beneficial HLA class I alleles (32 of the 41), 8 (40%) of the vaccinees and 1 (8%) of the placebo recipients were able to remain off ART for 22 weeks ( $\Delta$  32%, 80%CI [7.6; 55.7]); with pVL <2,000 copies/mL being observed in 5 and 1 vaccine and placebo recipients, respectively. Magnitude of HTI-specific responses at the time of ATI start positively correlated with time off ART in vaccinees (Rho 0.65,  $p<0.01$ ). Decay in total or intact HIV proviral DNA from baseline to ATI was similar between vaccine and placebo arms.

**Conclusion:** HTI vaccines were safe and highly immunogenic in early-treated PLWH with a prolonged time off ART seen in vaccinees with non-beneficial HLA class I alleles. Time off ART positively correlated with vaccine-induced HTI-specific T cell responses at ATI start. Multivariate analysis for other correlates of response is ongoing. These encouraging data strongly support the use of HTI-based vaccines as the backbone of combination cure regimens such as with the TLR7 agonist vesatolimod, which is currently being evaluated in the AELIX-003 study (NCT04364035).

## 162 NEURON DAMAGE AND RESERVOIR ARE SECONDARY TO HIV TRANSCRIPTS DESPITE SUPPRESSIVE ART

Kazuo Suzuki<sup>1</sup>, John Saunders<sup>1</sup>, Angeliqe Levert<sup>1</sup>, Shannen Butterly<sup>1</sup>, Zhixin Liu<sup>2</sup>, Takaomi Ishida<sup>3</sup>, Chin-Shiou Huang<sup>4</sup>, Thomas Gates<sup>1</sup>, Caroline Rae<sup>5</sup>, Lauriane Jugé<sup>6</sup>, Lucette A. Cysique<sup>1</sup>, Bruce Brew<sup>1</sup>

<sup>1</sup>St Vincent's Hospital, Sydney, Australia, <sup>2</sup>University of New South Wales, Randwick, Australia, <sup>3</sup>DENKA Life Innovation Research Institute, Tokyo, Japan, <sup>4</sup>PlexBio Research Development, Taipei, Taiwan, <sup>5</sup>Neuroscience Research Australia, Randwick, Australia

**Background:** HAND persists despite suppressive cART for reasons that are unclear. We have previously shown that transcription without whole virus may explain HAND and contribute to the CSF HIV reservoir. Here we confirm and extend these findings with double the number of patients using our highly sensitive Double-R assay of HIV RNA/DNA and flow cytometry for cellular origin.

**Methods:** DNA and RNA were extracted from cells in 20 paired samples of CSF and blood taken from HIV+ subjects (4 with current HAND and 2 with past HAND) on cART with both plasma and CSF HIV RNA (Roche) <50 copies/ml. HIV-1 transcripts and DNA levels were determined by the previously described Double-R assay based on the extremely sensitive  $\pi$ Code MicroDiscs platform. Immunological profiles of CSF cells and PBMC were compared by 18-colour flow cytometry. In vivo brain injury was assessed with MR spectroscopy in the frontal white matter (FWM), posterior cingulate cortex (PCC), and caudate area.

**Results:** 18/20 patients' CSF CD4+T cells had significantly higher levels of cell-associated HIV-1 RNA transcriptional activity vs PBMCs (median 8,331 copies/10<sup>6</sup> CD4+T cells, vs 680; p<0.0001), with significant correlation of transcriptional activity within CD4+T cells between CSF and PBMC (r=0.46; p=0.029). 16/20 patients also had significantly higher HIV-1 DNA levels in CSF CD4+T cells (median 3,940 copies/10<sup>6</sup> cells vs 885; p<0.0001). CSF transcriptional activity was inversely correlated with the neuronal integrity biomarker N-acetyl aspartate (NAA) in FWM (p=0.04) and PCC (p=0.055). Transcriptional activity in PBMCs showed similar results: NAA in FWM (p=0.051) and in PCC (p=0.047). CSF cells were 91% memory T cells, with roughly equal memory CD4 (median 3,605 cells) and CD8 T cells (3,507 cells). Other CSF cells were 3.1% CD14+CD16+ monocytes, 2.0% NK cells and 0.4% B cells. CXCR3+ CD49d+ integrin $\beta$ 7- cells were 76% of CSF CD4 T cells compared with 17% of CD4 in PBMC; 51% were CCR5+ (vs 16% in PBMC); and 18% expressed CD38 and/or HLA-DR activation markers (vs 11% in PBMC).

**Conclusion:** CSF is an HIV reservoir with high transcription activity despite ART. It is biologically significant because of compromised neuron integrity likely mediated by transcription products (tat). The cellular source of HIV RNA is most likely the predominant CXCR3+ CD49d+ integrin $\beta$ 7- CCR5+ memory CD4+T cells; monocytes may be less important. Therapies targeting transcription should be developed.

|         | HIV RNA Copies /10 <sup>6</sup> cells | HIV DNA Copies /10 <sup>6</sup> cells | Total CSF cell counts |                   |                      | % of CD4                          |              |                      |
|---------|---------------------------------------|---------------------------------------|-----------------------|-------------------|----------------------|-----------------------------------|--------------|----------------------|
|         |                                       |                                       | Median (IQR)          | Median (IQR)      | Median (IQR)         | Median (IQR)                      | Median (IQR) | Median (IQR)         |
|         | Median (IQR)                          | Median (IQR)                          | Memory CD4            | Memory CD8        | Monocytes CD14+CD16+ | CXCR3+ CD49d+ integrin $\beta$ 7- | CCR5+        | CD38+ and/or HLA-DR+ |
| CSF     | 8331 (4395-14511)                     | 3,940 (1547-11291)                    | 4,686 (1679-7587)     | 3,507 (1535-6560) | 414 (122-900)        | 76% (74-84)                       | 51% (47-59)  | 18% (12-22)          |
| PBMC    | 680 (657-1217)                        | 885 (718-3165)                        | N/A                   | N/A               | N/A                  | 17 (14-24)                        | 16 (11-20)   | 11 (7-14)            |
| p value | <0.0001                               | <0.0001                               | -                     | -                 | -                    | <0.0001                           | <0.0001      | <0.0001              |

## 163 3T BRAIN MRS REVEALS DISTINCT METABOLITE PATTERNS OF ART INITIATION DURING ACUTE HIV

Napapon Sailasuta<sup>1</sup>, Torie Tsuei<sup>2</sup>, Carlo Sacdalan<sup>3</sup>, Eugene Kroon<sup>3</sup>, Kultida Poltavee<sup>3</sup>, Nittaya Phanuphak<sup>3</sup>, Shayanne Martin<sup>2</sup>, Jintanat Ananworanich<sup>4</sup>, Victor Valcour<sup>2</sup>, Sandhya Vasani<sup>5</sup>, Mantana Pothiris<sup>6</sup>, Netsiri Dumrongpisutikul<sup>6</sup>, Serena S. Spudich<sup>7</sup>, Robert Paul<sup>8</sup>, for the SEARCH 010/RV254 Study Team

<sup>1</sup>University of Hawaii at Manoa, Honolulu, HI, USA, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA, <sup>3</sup>SEARCH, Bangkok, Thailand, <sup>4</sup>University of Amsterdam, Amsterdam, Netherlands, <sup>5</sup>US Military HIV Research Program, Silver Spring, MD, USA, <sup>6</sup>Chulalongkorn University, Bangkok, Thailand, <sup>7</sup>Yale University, New Haven, CT, USA, <sup>8</sup>University of Missouri St Louis, St Louis, MO, USA

**Background:** Our previous studies have documented cellular neuroinflammation in acute HIV infection (AHI) and normalization after six month of early initiation of ART measured by 1.5T MRI single voxel proton magnetic resonance spectroscopy (1H MRS), specifically in the gray matter

(basal ganglia, occipital gray, and frontal gray). We now explore the impact of early ART on white matter brain metabolism in AHI after two years of treatment using a 3T MRI, discriminating by variable timing of treatment initiation.

**Methods:** Thai acute HIV (AHI) participants enrolled in Bangkok, Thailand as part of the SEARCH 010/RV254 study completed 8-cc single voxel 1H MRS in the left frontal white matter (FWM) on a 3T MR scanner prior to ART onset (M0) and again after two years of ART (M24) initiated in Fiebig I-IV AHI. HIV negative (HC) participants were included for comparison. Brain metabolite levels were corrected for T1, T2, and CSF contribution within the MRS voxel. GraphPad Prism was used for statistical analysis. Two-tailed paired parametric T-tests were used to compare MRS outputs at baseline and two years after ART with Bonferroni correction.

**Results:** Thirty-seven male participants were categorized as Fiebig I-IV. There were no significant differences between brain metabolites at M0 compared to HC and AHI after cART (Table 1). At M0, participants with Fiebig I/II exhibited significantly lower tNAA, a marker of neuronal health, compared to HC, and showed a trend to normalization at M24. Among participants with Fiebig III/IV, tNAA was reduced at M24 compared to M0. In Fiebig I/II choline, the inflammation marker, was elevated at M24 compared to M0. Similar results were observed in Fiebig III/IV, where choline and myo-inositol were reduced at M24 compared to M0.

**Conclusion:** Participants with AHI that are in Fiebig stage III/IV show further brain metabolites declined compared to HC in white matter particularly cell generation markers, inflammation and glial dysfunction (choline, NAA, and myo-inositol) concurrent with the early initiation of ART in AHI after 2 years of treatment. Using the 4th generation immunoassay (Fiebig stages) to classified acute HIV infection may be beneficial measuring changes in frontal white matter brain metabolites levels after two years of ART.

Table 1: MRS results of AHI and HC before and after cART.

| WM MRS                     | HC         | AHI Fiebig Stages |             |                   |                 |                   |                   |
|----------------------------|------------|-------------------|-------------|-------------------|-----------------|-------------------|-------------------|
|                            |            | All AHI M0        | All AHI M24 | Stage I/II M0     | Stage I/II M24  | Stage III/IV M0   | Stage III/IV M24  |
| N                          | 25         | 37                | 37          | 10                | 10              | 27                | 27                |
| Age (years)                | 31 (19-43) | 26 (22-54)        |             |                   |                 |                   |                   |
| CD4 count (cells/ $\mu$ L) |            |                   |             | 429 (188-1302)    | 971 (397-2037)  | 359 (109-744)     | 658 (335-1357)    |
| Plasma HIV RNA (copies/mL) |            |                   |             | 5.8 (7.05-2.87)   | 1.3 (1.3)       | 6.5 (3.25-7.88)   | 1.3 (1.3)         |
| NP24 global score          |            |                   |             | 0.44 (-0.40-1.34) | 0.59 (0.32-1.3) | 0.06 (-1.44-1.60) | 0.95 (-2.20-1.78) |
| CD4> 500 (N)               |            | 11                | 11          | 5                 |                 | 6                 |                   |
| CD4/CD8> 1 (N)             |            | 10                | 10          | 7                 |                 | 3                 |                   |
| Glx (Glu+Gln)              | 2.08       | 2.1               | 1.97        | 1.97              | 1.94            | 2.11              | 2.02              |
| tNAA (NAA + NAAg)          | 1.95       | 1.81              | 1.75        | 1.57#             | 1.69            | 1.81              | 1.29*             |
| tCho (Cho+tPCho)           | 0.25       | 0.24              | 0.25        | 0.2               | 0.3##           | 0.24              | 0.16**            |
| ml (myo-inositol)          | 0.72       | 0.84              | 0.81        | 0.68              | 0.76            | 0.81              | 0.40***           |

\*,\*\*,\* Stage III/IV M0-M24 P < 0.0005

#, AHI-HC, P = 0.01

## Stage I/II M0-M24, P = 0.05

## 164 EFFECTS OF HIV AND AGING ON FUNCTIONAL CONNECTIVITY AND ANATOMY

Patrick H. Luekett<sup>1</sup>, Kayla Hannon<sup>1</sup>, John J. Lee<sup>1</sup>, Robert Paul<sup>2</sup>, Joshua S. Shimony<sup>1</sup>, Karin L. Meeker<sup>1</sup>, Sarah Cooley<sup>1</sup>, Beau M. Ances<sup>1</sup>

<sup>1</sup>Washington University in St Louis, St Louis, MO, USA, <sup>2</sup>University of Missouri St Louis, St Louis, MO, USA

**Background:** The effects of HIV infection and aging on brain structural and functional connectivity and neuropsychological performance (NP) remains poorly understood. Understanding the effects of the virus using a lifespan perspective is vital for providing appropriate care to people living with HIV (PLWH).

**Methods:** 297 virologically well-controlled (<200 copies/mL) PLWH (mean age 48.5y, 67% male) on cART and 1509 HIV uninfected (HIV-) controls (mean age 45.4y, 62% male) matched for age, sex, and education were evaluated. All participants completed structural and functional neuroimaging. PLWH were

classified as cognitively normal (HIVCN) or impaired (HIVCI) based on NP battery consisting of five domains. Relief feature selection identified the strongest predictive functional resting state networks (RSNs) with regards to HIV serostatus and degree of cognitive impairment within specific age bins (< 35, 35-55, and >55 years old). Deep learning models identified where the largest structural differences occurred in relation to the identified RSNs.

**Results:** The Relief algorithm identified the strongest predictive RSNs of HIV status between HIV- controls and HIVCN as the salience (SAL) and parietal memory network (PMN). The strongest predictive RSNs of HIV status between HIV- controls and HIVCI were the SAL, PMN, and frontal parietal (FPN). The strongest predictive RSNs of HIV cognitive impairment status between HIVCN and HIVCI were the SAL, FPN, and ventral attention (VAN). When evaluating different age bins, FPN became a stronger predictor with age, SAL and VAN lost predictive strength, and PMN remained consistent. With structural neuroimaging, the primary differences in RSN topology occurred in cortical and subcortical regions, including the dorsal and rostral lateral prefrontal cortex (Figure 1), anterior cingulate, and caudate.

**Conclusion:** We have identified RSNs that discriminated HIV-, HIVCN, and HIVCI using machine learning. Our results suggest PMN and SAL are highly impacted by HIV, and additional involvement of FPN leads to increased cognitive impairment. Deep learning models identified where the largest differences in RSN topology occurred. When evaluating different age bins, variability in RSNs predictive strength was observed, even under viral suppression. These results suggest a complex set of RSN and structural changes that are unique to HIV status, aging, cognitive impairment status, and anatomy.

165



**DIVERGENT AND SELF-REACTIVE IMMUNE RESPONSES IN THE CNS OF COVID-19 PATIENTS**

**Eric Song**<sup>1</sup>, Christopher Bartley<sup>2</sup>, Ryan Chow<sup>1</sup>, Thomas Ngo<sup>2</sup>, Ruoyi Jiang<sup>1</sup>, Colin Zamecnik<sup>2</sup>, Ravi Dandekar<sup>2</sup>, Lindsay McAlpine<sup>1</sup>, Serena S. Spudich<sup>1</sup>, Joseph DeRisi<sup>2</sup>, Akiko Iwasaki<sup>1</sup>, Samuel Pleasure<sup>2</sup>, Michael Wilson<sup>2</sup>, Shelli F. Farhadian<sup>1</sup>, for the Yale IMPACT Team

<sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** One third of COVID-19 patients develop significant neurological symptoms, yet SARS-CoV-2 is rarely detected in central nervous system (CNS) tissue, suggesting a potential role for parainfectious processes, including neuroimmune responses.

**Methods:** We examined immune parameters in CSF and blood samples from a cohort of hospitalized patients with COVID-19 and significant neurological complications (n=6), compared to SARS-CoV-2 uninfected controls (Fig1A). Immune cells were characterized by single cell RNA and repertoire sequencing. Intrathecal antibodies were assessed for anti-viral and auto-reactivity by ELISA, mouse brain immunostaining, phage display, and IP-MS.

**Results:** Through single cell and parallel cytokine analyses of CSF and paired plasma, we found divergent T cell responses in the CNS compartment, including increased levels of IL-1B and IL-12-associated innate and adaptive immune cell activation (Fig1B). We found evidence of clonal expansion of B cells in the CSF, with B cell receptor sequences that were unique from those observed in peripheral blood B cells (Fig1C), suggesting a divergent intrathecal humoral response to SARS-CoV-2. Indeed, all COVID-19 cases examined had anti-SARS-CoV-2 IgG antibodies in the CSF whose target epitopes diverged from serum antibodies. Next, we directly examined whether CSF resident antibodies targeted self-antigens and found a significant burden of CNS autoimmunity, with the CSF from most patients recognizing neural self-antigens. COVID-19 CSF produced immunoreactive staining of specific anatomic regions of the brain including cortical neurons, olfactory bulb, thalamus, and cerebral vasculature. Finally, we produced a panel of monoclonal antibodies from patients' CSF and peripheral blood, and show that these target both anti-viral and anti-neural antigens-including one CSF-derived mAb specific for the spike protein that also recognizes neural tissue (Fig1D).

**Conclusion:** This immune survey reveals evidence of a compartmentalized and self-reactive immune response in the CNS in COVID-19 patients with neurologic symptoms. We identified both innate and adaptive anti-viral immune responses, as well as humoral autoimmunity that appears to be unique to the CNS during SARS-CoV-2 infection. These data suggest a potential role for autoimmunity in contributing to neurological symptoms, and merit further investigation to the potential role of autoantibodies in post-acute COVID-19 neurological symptoms.

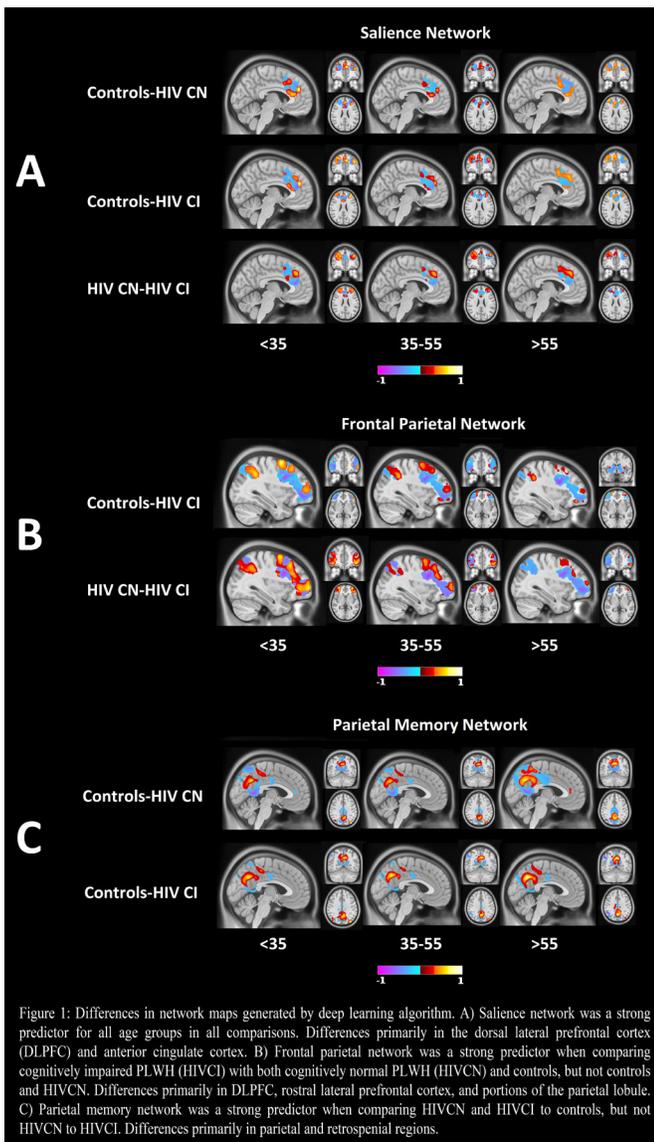
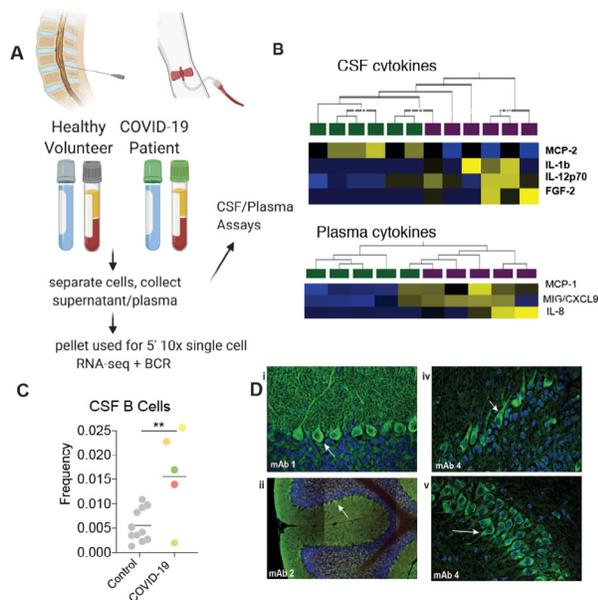


Figure 1: Differences in network maps generated by deep learning algorithm. A) Salience network was a strong predictor for all age groups in all comparisons. Differences primarily in the dorsal lateral prefrontal cortex (DLPFC) and anterior cingulate cortex. B) Frontal parietal network was a strong predictor when comparing cognitively impaired PLWH (HIVCI) with both cognitively normal PLWH (HIVCN) and controls, but not controls and HIVCN. Differences primarily in DLPFC, rostral lateral prefrontal cortex, and portions of the parietal lobule. C) Parietal memory network was a strong predictor when comparing HIVCN and HIVCI to controls, but not HIVCN to HIVCI. Differences primarily in parietal and retrosplenial regions.

**Figure:** A. Study design. B. Hierarchical clustering of cytokines increased (yellow) in the CSF (top) and plasma (bottom) of COVID-19 patients (purple) compared to controls (green). C. CSF of COVID-19 patients contains an increased frequency of B cells when compared to CSF from controls. D. Mouse brain immunostaining of monoclonal antibodies generated from COVID-19 patient CSF demonstrating reactivity to brain tissue. mAb2 is also reactive against the SARS-CoV-2 spike protein.



## 166 CHROMOSOMAL COPY NUMBER ALTERATIONS IN ANAL PRECANCERS FROM PEOPLE WITH HIV

Tinaye Mutetwa<sup>1</sup>, Rosa Karlic<sup>2</sup>, Jane Houldsworth<sup>3</sup>, Anne M. Bowcock<sup>3</sup>, Michael M. Gaisa<sup>3</sup>, Yuxin Liu<sup>3</sup>, Paz Polak<sup>3</sup>, Keith Sigel<sup>3</sup>

<sup>1</sup>Icahn School of Medicine at Mount Sinai, New York City, NY, <sup>2</sup>University of Zagreb, Zagreb, Croatia, <sup>3</sup>Icahn School of Medicine at Mount Sinai, New York City, NY, USA

**Background:** People living with HIV (PWH) are susceptible to high-risk human papillomavirus (HPV) infection of the anal canal owing to their immunocompromised status. The virus can transform anal squamous epithelia to low-grade squamous intraepithelial lesions (LSILs) and further to high-grade squamous intraepithelial lesions (HSILs). HSILs are well-defined cancer precursors that can progress to invasive cancer if left untreated. HPV-associated cancers commonly carry genomic abnormalities, specifically, a gain of chromosome 3q26 (PIK3CA), 20q13, 5p15 (TERT) and 7 centromere (cen7). We aimed to determine whether HPV-associated anal precancers carry similar genomic abnormalities and if so, to analyze their associations with histological severity and specific HPV types.

**Methods:** Anal lesions from 63 unique patients (36 HSIL, 27 LSIL) were obtained via high-resolution anoscopy (HRA)-directed biopsy. Anal swabs were performed at the time of HRA to collect samples for cytological diagnosis and HPV DNA testing of HPV16, 18, and other (12) high-risk types. FISH-based HPV-associated Cancer Test (FHACT) was performed on the biopsy samples using four-color probes to detect any gain of chromosome 3q, 20q, 5p, and 7. The associations between genomic alterations, histological severity and HPV types were analyzed.

**Results:** Our cohort had a median age of 50, was predominantly (70%) of Black and Hispanic race/ethnicity and 95% had suppressed HIV viral loads. Genomic abnormalities were detected in 47% of anal HSILs and 7% of LSILs (p=0.002). A gain of 3q, 20q, 5p, and cen7 was detected in 42%, 31%, 31%, and 19% of HSILs and 7%, 4%, 0%, and 0% of LSILs, respectively. Genomic abnormalities were more frequent in lesions associated with HPV16/18 infection, compared with those associated with non-16/18 types and negative HPV (42% vs. 24% vs. 9%; p=0.06). 91% of lesions with 5p gain had gain in 20q. Cen7 gains were only detected in lesions with a gain of 20q13, suggesting a possible sequential order in development of chromosomal gains: 3q26 first, followed by 20q13 or 5p15, and then cen7.

**Conclusion:** Anal precancers frequently demonstrate genomic abnormalities found in other HPV-associated cancers. The most common abnormality was

the amplification of chromosome 3q, the location of PIK3CA gene. Our results suggest that PI 3-kinase/AKT signaling pathway may play an important role in anal cancer development in PWH.

| Table: Characteristics by Lesion Grade    |              |              |         |
|---|--------------|--------------|---------|
|   | HSIL<br>n=36 | LSIL<br>n=27 | p-value |
| <b>Histologic Biopsy Result</b>           |              |              |         |
| AIN 1                                     | 0            | 27 (100%)    |         |
| AIN 2                                     | 25 (69%)     | 0            |         |
| AIN 3                                     | 11 (31%)     | 0            |         |
| <b>Concurrent High-Risk (HR) HPV Type</b> |              |              |         |
| HR HPV 16 and/or 18                       | 21 (58%)     | 3 (11%)      | <0.001  |
| Other HR HPV                              | 10 (28%)     | 11 (41%)     |         |
| HPV-negative                              | 1 (3%)       | 10 (37%)     |         |
| Missing                                   | 4 (11%)      | 3 (11%)      |         |
| <b>Concurrent Pap Result</b>              |              |              |         |
| Benign                                    | 3 (8%)       | 3 (11%)      | 0.1     |
| ASCUS                                     | 14 (39%)     | 16 (59%)     |         |
| LSIL                                      | 11 (31%)     | 5 (19%)      |         |
| HSIL                                      | 5 (14%)      | 0            |         |
| Missing                                   | 3 (8%)       | 3 (11%)      |         |
| <b>FISH Result</b>                        |              |              |         |
| Normal                                    | 20 (53%)     | 25 (93%)     | 0.002   |
| Abnormal                                  | 17 (47%)     | 2 (7%)       |         |
| 3q26 (PIK3CA)                             | 15           | 2            |         |
| 5p15 (TERT)                               | 11           | 0            |         |
| 20q13                                     | 11           | 1            |         |
| Cen7                                      | 7            | 0            |         |

AIN: Anal intraepithelial neoplasia; HR HPV: High-risk human papilloma virus; HSIL: High-grade intraepithelial lesion; LSIL: Low-grade intraepithelial lesion.

## 167 POMALIDOMIDE AND LIPOSOMAL DOXORUBICIN FOR KAPOSI SARCOMA +/- OTHER KSHV DISEASES

Ramya Ramaswami<sup>1</sup>, Kathryn Lurain<sup>1</sup>, Anaida Widell<sup>1</sup>, Priscila Goncalves<sup>1</sup>, Irene Ekweke<sup>1</sup>, William D. Figg<sup>1</sup>, Cody Peer<sup>1</sup>, Ralph Mangusan<sup>1</sup>, Jomy George<sup>1</sup>, Seth Steinberg<sup>1</sup>, Denise Whitby<sup>2</sup>, Thomas S. Uldrick<sup>1</sup>, Robert Yarchoan<sup>1</sup>

<sup>1</sup>National Cancer Institute, Bethesda, MD, USA, <sup>2</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA

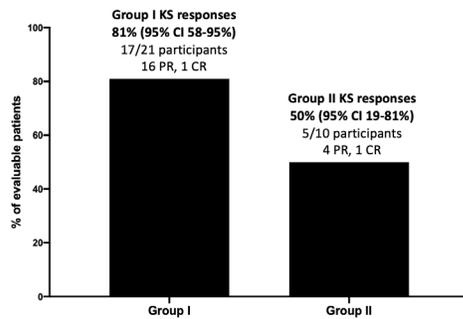
**Background:** Kaposi sarcoma herpesvirus (KSHV, also known as human herpesvirus 8 [HHV-8]), is the causative agent of Kaposi sarcoma (KS), a multicentric angioproliferative tumor, and other diseases including a form of multicentric Castleman disease (KSHV-MCD) and KSHV inflammatory cytokine syndrome (KICS). KS can be difficult to treat when it occurs with KSHV-MCD or KICS; resulting in high mortality rates. Liposomal doxorubicin (dox), a chemotherapy, and pomalidomide (pom), an immunomodulatory drug, are FDA-approved therapies for KS. The safety and activity of the combination (pom/dox) in KS alone or with KSHV-associated diseases are unknown.

**Methods:** The primary objective of this Phase I/II study was to evaluate safety and tolerability of pom/dox in 2 groups of participants with KS requiring systemic therapy: Group I (G1) - KS alone; Group II (G2) - KS with concurrent KSHV-MCD or KICS. Patients received dox at 20 mg/m<sup>2</sup>, intravenously on day 1 of a 28-day cycle combined with pom once daily on days 1 to 21 at escalating dose levels (DL) (I - 2mg, II - 3mg, or III - 4mg) in a 3+3 design until plateau of response or other pre-specified criteria. Participants received 81mg of aspirin daily as thromboprophylaxis. KS responses were evaluated using the modified AIDS Clinical Trial Group criteria.

**Results:** Thirty-four cisgender men, all with severe (T1) KS [21 patients (62%) in G1 and 13 patients (38%) in G2] were treated; 32 (94%) were HIV-infected and 22 (65%) had prior chemotherapy for KS (15/21 G1 and 7/13 G2). All participants with HIV were on antiretroviral therapy with a baseline median CD4 count of 217 cells/ $\mu$ L (interquartile range (IQR): 85-362) and median HIV VL of 24 copies/ml (IQR: <20 - 134). There were no dose-limiting toxicities (DLTs) at DLIII for G1, and additional participants were treated at the maximum tolerated dose of 4mg of pom. In G2, grade 3 rash and pharyngeal edema were DLTs observed at 3mg of pom (DLII). A median of 6 cycles (IQR: 2-11) were administered; the most common CTCAE grade 3/4 toxicity was neutropenia. Among evaluable participants receiving >2 cycles, 17/21 patients in G1 had a response (16 partial and 1 complete) (81% [95% confidence interval (CI) 58-95%]) and 5/10 patients in G2 had a response (4 partial and 1 complete) (50% [95% CI 19-81%], Figure 1).

**Conclusion:** Pom/dox was well-tolerated and active in heavily pretreated participants with KS alone. Among participants with KS and KSHV-MCD or KICS, activity was noted but pom/dox was less well-tolerated.

Figure 1: Response by Group



168 VAGINAL PH PREDICTS CERVICAL INTRAEPITHELIAL NEOPLASIA-2 REGRESSION IN HIV+ WOMEN

**Katherine G. Michel<sup>1</sup>**, Christine Colie<sup>1</sup>, Robert Burk<sup>2</sup>, L. Stewart Massad<sup>3</sup>, Cuiwei Wang<sup>1</sup>, Charbel Moussa<sup>1</sup>, Gypsyamber D'Souza<sup>4</sup>, Lisa Rahangdale<sup>5</sup>, Lisa Flowers<sup>6</sup>, Joel Milam<sup>7</sup>, Joel Palefsky<sup>8</sup>, Howard Minkoff<sup>9</sup>, Howard Strickler<sup>2</sup>, Seble Kassaye<sup>1</sup>  
<sup>1</sup>Georgetown University, Washington, DC, USA, <sup>2</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>3</sup>Washington University in St Louis, St Louis, MO, USA, <sup>4</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>Emory University, Atlanta, GA, USA, <sup>7</sup>University of Southern California, Los Angeles, CA, USA, <sup>8</sup>University of California San Francisco, San Francisco, CA, USA, <sup>9</sup>Maimonides Medical Center, Brooklyn, NY, USA

**Background:** We previously reported that persistence/progression of cervical intraepithelial neoplasia-2 (CIN2) was uncommon in women living with HIV (WLH) from the Women's Interagency HIV Study (WIHS, now MWCCS). Here we examined additional factors that may influence CIN2 natural history.

**Methods:** A total of 337 samples from 94 WLH with a confirmed CIN2 diagnosis were obtained from the MWCCS. 42 cervicovaginal HPV types and 34 cervicovaginal cytokines/chemokines were measured at CIN2 diagnosis (94 samples) and 6-12 months prior to CIN2 diagnosis (79 samples). Covariates, including CD4 count and vaginal pH, were abstracted from core MWCCS visits. Logistic regression models were used to explore CIN2 regression (CIN1, normal) vs. persistence/progression (CIN2, CIN3). Log rank tests, Kaplan Meier method, and Cox regression modeling were used to determine CIN2 regression rates.

**Results:** Participants were predominantly African American (53.2%) and using antiretroviral therapy (66.0%). The most prevalent HPV types across all visits were HPV54 (21.6%) and 53 (21.3%); most prevalent high-risk (hr)-HPV types were 58 (18.4%) and 16 (17.5%). 33 women (35.1%) with incident CIN2 had a subsequent CIN2/CIN3 diagnosis during the study period (median 12.5 years of follow-up). Women who regressed had a higher CD4 T cell count at CIN2 diagnosis (Mann Whitney p=0.02). Each additional hr-HPV type detected at the pre-CIN2 visit was associated with increased odds of CIN2 persistence/progression (OR 2.27, 95% CI 1.15, 4.50). Higher vaginal pH (aOR 2.27, 95% CI 1.15, 4.50) and bacterial vaginosis (aOR 5.08, 95% CI 1.30, 19.94) at the CIN2 diagnosis visit were associated with higher odds of CIN2 persistence/progression. Vaginal pH >4.5 at CIN2 diagnosis was also associated with unadjusted time to CIN2 persistence/progression (log rank p=0.002) and a higher rate of CIN2 persistence/progression (adjusted hazard ratio [aHR] 3.37, 95% CI 1.26, 8.99). Cervicovaginal cytokine/chemokine levels were not associated with CIN2 persistence/progression. Evaluating women who did not receive CIN2 treatment, vaginal pH remained associated with increased odds of CIN2 persistence/progression (OR 2.46, 95% CI 1.19, 5.13). Adjusting for CVL storage time, self-reported STI status, or CVL contaminants did not affect results.

**Conclusion:** We found relatively low prevalence of HPV16/18 in this cohort. Elevated vaginal pH at the time of CIN2 diagnosis may be a useful indicator of CIN2 persistence/progression and the rate of persistence/progression.

169 WILMS' TUMOR 1 IS OVEREXPRESSED IN KAPOSI SARCOMA AND IS REGULATED BY VFLIP/K13

**Ayana Morales<sup>1</sup>**, Caitlyn Genovese<sup>1</sup>, Matthew Bott<sup>1</sup>, Julio Alvarez<sup>2</sup>, Sung Soo Mun<sup>3</sup>, Jennifer Totonchy<sup>4</sup>, Jesus Delgado<sup>5</sup>, Stephanie Chang<sup>6</sup>, Maite Ibañez de Garayo<sup>1</sup>, David Scheinberg<sup>3</sup>, Paul Rubinstein<sup>7</sup>, Thomas Campbell<sup>8</sup>, Margaret Borok<sup>9</sup>, Susan Krown<sup>10</sup>, Ethel Cesarman<sup>1</sup>

<sup>1</sup>Weill Cornell Medicine, New York, NY, USA, <sup>2</sup>SUNY Downstate Medical Center, Brooklyn, NY, USA, <sup>3</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA, <sup>4</sup>Chapman University, Irvine, CA, USA, <sup>5</sup>Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, <sup>6</sup>Cornell University, Ithaca, NY, USA, <sup>7</sup>Rush University Medical Center, Chicago, IL, USA, <sup>8</sup>University of Colorado, Aurora, CO, USA, <sup>9</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>10</sup>AIDS Malignancy Consortium, New York, NY, USA

**Background:** Kaposi Sarcoma (KS), a vascular neoplasm caused by Kaposi sarcoma herpesvirus (KSHV, also called HHV-8), is the most common HIV associated malignancy globally. A National Cancer Institution (NCI) Prioritization Summit ranked Wilms' Tumor 1 'WT1' as the #1 tumor associated antigen to direct immunotherapy towards. Various forms of WT1 immunotherapies are in development. Following on our early data showing WT1 upregulation in KS in 46 cases (CROI 2019), we assessed WT1 expression in KS in an expanded cohort, and determined if KSHV infection accounts for this upregulation. Among the KSHV genes, we focused on vFLIP because of its ability to induce NF-κB, a transcription factor known to affect WT1 levels.

**Methods:** We used immunohistochemistry analysis to evaluate 303 biopsies of advanced HIV associated KS from clinical trial AMC066/A5263 for expression of WT1, LANA, the presence of CD4+ and CD8+ T cells. We examined effects of KSHV on WT1 expression in vitro using endothelial cell infection models, and determined whether a single latent viral gene, vFLIP, influences WT1 expression. We knocked down WT1 using WT1 lentiviral shRNA. We then tested a T cell receptor mimic antibody, ESK-1, specific for WT1 peptide/HLA-A02 expression, for its ability to bind KSHV-infected or vFLIP-expressing endothelial cells

**Results:** Moderate to strong WT1 expression (>20% WT1 positive cells) was found in 64.1% of the 303 biopsies, and in 92.3% of nodular lesions. WT1 expression correlated with increased histopathologic stage, expression of the viral latent oncoprotein (LANA; r=0.687, p=0.0001), and was inversely correlated with the quantity of CD8+ T cells (r=-0.2536 p=0.0001). In vitro, KSHV infection of endothelial cells resulted in upregulation of WT1. We found that vFLIP expression alone upregulates WT1 and appears dependent on NF-κB. Flow cytometry using ESK-1 antibodies, showed increased binding to endothelial cells with KSHV infection or vFLIP expression compared to mock infected or uninduced endothelial cells. WT1 loss in KSHV-infected endothelial cells in vitro appears to associate with decreased vFLIP and LANA expression.

**Conclusion:** WT1 is overexpressed in Kaposi sarcoma and is upregulated by vFLIP/K13. Our data demonstrate increased binding of WT1 overexpressing endothelial cells by ESK-1, a human monoclonal antibody in preclinical development as adjuvant immunotherapy directed towards WT1 overexpressing malignancies. Immunotherapy directed towards WT1 may prove as a new treatment strategy in KS.

170 INFLAMMASOME ACTIVATION IN PATIENTS WITH KSHV-ASSOCIATED DISORDERS

**Ramy Ramaswami<sup>1</sup>**, Silvia Lage<sup>2</sup>, Kathryn Lurain<sup>1</sup>, Joseph Rocco<sup>2</sup>, Maura Manion<sup>2</sup>, Robert Yarchoan<sup>1</sup>, Irini Sereti<sup>2</sup>

<sup>1</sup>National Cancer Institute, Bethesda, MD, USA, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

**Background:** Kaposi sarcoma herpesvirus (KSHV) causes several disorders: Kaposi sarcoma (KS), primary effusion lymphoma (PEL), a plasmablastic form of multicentric Castleman disease (MCD) and most recently inflammatory cytokine syndrome (KICS), which may occur alone or concurrently in the same patient. These conditions occur among people living with HIV. KSHV-associated disorders (KAD) are characterized by elevated plasma levels of inflammatory mediators, resulting in systemic symptoms, which if not identified and treated can result in high mortality. Activation of the inflammasome, which leads to pro-inflammatory cytokines such as IL-1β and IL-18 via active caspase-1, has not been assessed in patients with KAD.

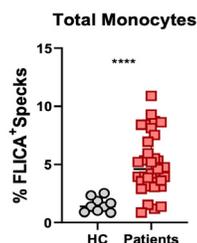
**Methods:** Peripheral blood mononuclear cells (PBMCs) from 9 healthy controls (HCs) and 33 participants with KAD [PEL (5), MCD (9), KS (6), KICS (6) or overlap of these conditions (7)] were incubated with a probe to assess active caspase-1 (FLICA) followed by staining for ASC (apoptosis associated speck like protein

containing CARD) specks in peripheral monocytes to detect inflammasomes with active caspase-1. T-test and Wilcoxon rank sum tests were used to assess differences in speck formation and plasma cytokine levels between HC and KAD participants.

**Results:** Samples were obtained from 33 cisgender HIV-infected men with KAD (median (med) age 44 years; med CD4 count: 250 cells/ $\mu$ L, med HIV VL <50 copies/mL) and 9 HCs. KAD participants had higher IL-18 plasma levels than HCs (median: 2959 vs. 794 pg/mL,  $p=0.0009$ ), indicating that KAD are accompanied by systemic inflammasome activation. We also found higher levels of monocytes demonstrating spontaneous FLICA+ASC-speck formation in those with KAD compared to HCs (KAD: 89,546 cells/mL, 4.60% vs HCs: 30,965 cells/mL, 1.39%,  $p=0.0002$  and  $p<0.0001$ , Figure 1). While there were higher levels of classical CD14<sup>high</sup>CD16<sup>-</sup> monocyte subsets in the majority of KAD participants, those with MCD alone and PEL alone also had evidence of FLICA+ASC-specks inside the intermediate (CD14<sup>high</sup>CD16<sup>-</sup>) and patrolling (CD14<sup>low</sup>CD16<sup>+</sup>) monocyte subsets, respectively. Overall, as compared to participants with one KAD, those with more than one KAD did not have significantly different monocytes with FLICA+ASC-specks/mL ( $p=0.09$ ).

**Conclusion:** Our data suggest that activation of the inflammasome in circulating blood monocytes contributes to the pathogenesis of KSHV-associated disorders and could potentially represent a target for host-directed therapy against these diseases.

**Figure 1: Percentage of Monocytes with FLICA\*Specks**



## 171 COVID-19 INFECTION IN HIGH-RISK SOUTH AFRICAN PREGNANCIES WITH AND WITHOUT HIV

**Liesl De Waard**<sup>1</sup>, Eduard J. Langenegger<sup>1</sup>, Kobie Erasmus<sup>1</sup>, Tian Van der Merwe<sup>1</sup>, Nicolene Du Toit<sup>1</sup>, Chane Paulsen<sup>1</sup>, Nontando S. Nkangana<sup>1</sup>, Susanna E. Olivier<sup>1</sup>, Sonja Schell<sup>1</sup>, Magriet Van Niekerk<sup>1</sup>, Jantjie J. Taljaard<sup>1</sup>, Angela Dramowski<sup>1</sup>, Cathy A. Cluver<sup>1</sup>, Adrie Bekker<sup>1</sup>

<sup>1</sup>Stellenbosch University, Tygerberg, South Africa

**Background:** Data from Africa reporting the outcomes of COVID-19 infection in pregnancy are limited, particularly for women with high-risk pregnancies (hypertension, diabetes and obesity) and pregnant women living with HIV (PLHIV). We describe the clinical features, maternal and birth outcomes of COVID-19 high-risk pregnancies at a South African tertiary care referral hospital with a 24% antenatal HIV prevalence.

**Methods:** We prospectively collected data from COVID-19 infected pregnant women attending the high-risk obstetric service at Tygerberg Hospital, Cape Town, between 1 May 2020 and 31 July 2020, and documented pregnancy and birth outcomes until 30 October 2020. Laboratory testing for SARS-CoV-2 infection was performed only in symptomatic pregnant women. Descriptive analysis was performed for all COVID-19 infected women with high-risk pregnancies; demographic and outcome variables were compared for PLHIV versus pregnant women without HIV.

**Results:** One hundred pregnant women (72 without HIV and 28 PLHIV) had laboratory-confirmed COVID-19 infection (Table 1). Obesity, hypertensive disorders and gestational diabetes were frequent comorbidities. Among 28 PLHIV, the majority received antiretroviral treatment 27 (96%); median CD4 count was 441 (14–838) cell/mm<sup>3</sup> for 21 (75%) and 19 (73%) were virologically suppressed. COVID-19 infection was diagnosed predominantly in the 3rd trimester (81%); 50% of women delivered within 2 weeks of infection onset. Forty women developed pneumonia; 13 developed adult respiratory distress syndrome (ARDS) and 6 required invasive ventilation. Eight women died, 7 from ARDS and 1 from advanced HIV disease with bacteraemia. Pregnancy outcomes included 91 live births (including 5 sets of twins), 5 stillbirths, 4 miscarriages, 2 mothers who died with the fetus in situ and 1 medical termination of pregnancy. Birth outcomes for 2 women were unknown. Outcome for the 91

liveborn neonates were good except for one who died from complications related to perinatal asphyxia. No significant differences for COVID-19 infection impact and outcome were noted for PLHIV versus those without HIV.

**Conclusion:** In this cohort of high-risk pregnant women with COVID-19 infection, no clinical differences in outcome attributable to HIV-infection were noted, however the majority of PLHIV were virally suppressed. The impact of COVID-19 infection in pregnancy was severe (40% complicated by pneumonia; 8% crude mortality rate); neonatal outcomes were favourable.

**Table 1. Characteristics and outcomes of high-risk COVID-19 pregnancies at Tygerberg Hospital by HIV status (n=100)**

|   | All pregnant women<br>N=100 | Pregnant women without HIV<br>n=72 | Pregnant women with HIV<br>n=28 | p-value |
|---|-----------------------------|------------------------------------|---------------------------------|---------|
| Age in years, median (IQR)                            | 31 (27–37)                  | 31 (27–37)                         | 34 (28–39)                      | 0.08    |
| Pre-existing medical conditions                       |                             |                                    |                                 |         |
| Chronic hypertension (%)                              | 22 (22)                     | 19 (26)                            | 3 (11)                          | 0.07    |
| Severe Obesity: BMI $\geq$ 40 (%) <sup>1</sup>        | 36/81 (44)                  | 28/59 (48)                         | 8/22 (36)                       | 0.37    |
| Obstetric conditions                                  |                             |                                    |                                 |         |
| Gestational hypertension                              | 18 (19)                     | 13 (18)                            | 5 (18)                          | 0.98    |
| Preeclampsia  | 24 (24)                     | 18 (25)                            | 6 (21)                          | 0.70    |
| Gestational diabetes                                  | 14(14)                      | 12 (17)                            | 2 (7)                           | 0.18    |
| COVID-19 diagnosis in gestational weeks, median (IQR) | 32 (29–37)                  | 32 (29–37)                         | 35 (30–38)                      | 0.27    |
| COVID-19 related complications                        |                             |                                    |                                 |         |
| Pneumonia (%)   | 40 (40)                     | 27 (38)                            | 13 (47)                         | 0.41    |
| ARDS (%)  | 13 (13)                     | 8 (11)                             | 5 (18)                          | 0.28    |
| ICU admission (%)                                     | 15 (15)                     | 9 (13)                             | 6 (21)                          | 0.35    |
| Outcomes  |                             |                                    |                                 |         |
| Live births (%)                                       | 91 (91)                     | 66 (92)                            | 25 (89)                         | 0.58    |
| Maternal mortality (%)                                | 8 (8)                       | 6 (8)                              | 2 (7)                           | 0.60    |

IQR, interquartile range; BMI, body mass index; ARDS, Adult Respiratory Distress Syndrome; ICU, intensive care unit or Obstetric Critical Care Unit

<sup>1</sup>BMI only available for 81 pregnant women

## 172 CHARACTERISATION OF SARS-CoV-2-INFECTED CHILDREN DEVELOPING NEUTRALISING ANTIBODIES

**Alessandra Ruggiero**<sup>1</sup>, Nicola Cotugno<sup>1</sup>, Bonfante Francesco<sup>2</sup>, Maria Raffaella Petrarà<sup>3</sup>, Giuseppe R. Pascucci<sup>1</sup>, Veronica Santilli<sup>1</sup>, Emma Manno<sup>1</sup>, Carlo Concato<sup>1</sup>, Giulia Linardos<sup>1</sup>, Daniele Donà<sup>4</sup>, Carlo Giaquinto<sup>4</sup>, Petter Brodin<sup>5</sup>, Paolo Rossi<sup>1</sup>, Anita De Rossi<sup>4</sup>, Paolo Palma<sup>1</sup>

<sup>1</sup>Bambino Gesù Children's Hospital, Rome, Italy, <sup>2</sup>Istituto zooprofilattico delle Venezie, Legnaro, Italy, <sup>3</sup>University of Padova, Padua, Italy, <sup>4</sup>University of Padova, Padova, Italy, <sup>5</sup>Karolinska Institute, Stockholm, Sweden

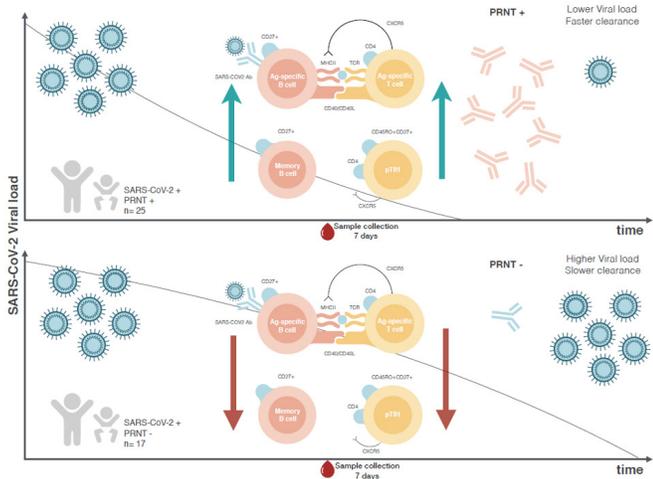
**Background:** Further knowledge on adaptive immunity to SARS-CoV-2 (CoV-2) in children is needed in order to define possible immunization strategies and reconsider pandemic control measures. We analyzed anti-CoV-2 antibodies (Ab) and their neutralizing activity (PRNT), alongside antigen (Ag) specific cellular response, in relation to virus load in nasopharyngeal swabs.

**Methods:** We analysed 42 CoV-2 patients at 7 days after symptoms onset. CoV-2 viral load (VL) was measured by RT-PCR and digital droplet PCR on longitudinal samples of nasopharyngeal swabs (NP). Virus infectivity (FFU) was tested by virus focus forming assay. CoV-2 antibodies were investigated by Diasorin (CoV-2 Ab) and neutralization assay (PRNT). CoV-2-specific CD4-CD40L+ T-cells and Spike specific B-cells were analysed by flow cytometry. Plasma proteomic profiling was measured by 2 Olink panels. We calculated the area under the curve (AUC) of the viral load from NP collected every 48 hours up to undetectable VL. Mann-Whitney was used to compare means in individuals with neutralizing activity (PRNT+) or not (PRNT-); linear regression was used to evaluate the associations between virus load and infectivity over time. Principal component analysis (PCA) was used to analyse proteomic data.

**Results:** Higher VL was found in seronegative patients expressed in terms of both CoV-2 Ab ( $p=0.003$ ) and PRNT ( $p=0.0007$ ). Similarly, lower FFU was associated with higher CoV-2 Ab ( $p=0.003$ ;  $\rho=-0.67$ ) and PRNT ( $p=0.023$ ;  $\rho=-0.46$ ). Further, the AUC of the viral load in NP showed an inverse correlation with CoV-2 Ab ( $p=0.031$ ;  $\rho=-0.54$ ). Development of humoral response was associated with the presence of CoV-2 specific IgD-CD27+ B cells, with a higher frequency of CoV-2 specific B cells found in seropositive compared to seronegative ( $p=0.001$ ). Besides, individuals developing neutralizing Ab had higher frequency CD4-CD40L+ T-cells compared to PRNT- ( $p=0.03$ ). The plasma proteome confirmed the association between cellular and humoral CoV-2

immunity, with PRNT+ showing higher viral signal transduction molecules (SLAMF1, CD244, CLEC4G).

**Conclusion:** This work provides a virological and immunological characterization of SARS-CoV-2 infected children presenting a differential Ab-mediated neutralizing activity. It demonstrates that children with neutralizing antibodies present reduced viral load, faster virus clearance and lower in vitro infectivity. These data provide information that can drive vaccination endpoints and quarantine measures policies.



**173 PEDIATRIC AND ADOLESCENT HIV TESTING AND DIAGNOSIS IN THE CONTEXT OF COVID-19**

**Jessica M. Gross<sup>1</sup>, Susan Hrapcak<sup>1</sup>, Emilia Rivadeneira<sup>1</sup>, Meena Srivastava<sup>2</sup>, Michael Grillo<sup>3</sup>, Gurpreet Kindra<sup>4</sup>, Jacobus Olivier<sup>4</sup>, Maria Deus<sup>5</sup>, Nelly Honwana<sup>5</sup>, Esther Nazziwa<sup>6</sup>, Madina Apolot<sup>6</sup>, Magdalene Mayer<sup>7</sup>, Amy Medley<sup>1</sup>**  
<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>United States Agency for International Development, Washington, DC, USA, <sup>3</sup>Defense Health Agency, San Diego, CA, USA, <sup>4</sup>Centers for Disease Control and Prevention, Pretoria, South Africa, <sup>5</sup>Centers for Disease Control and Prevention, Maputo, Mozambique, <sup>6</sup>Centers for Disease Control and Prevention, Kampala, Uganda, <sup>7</sup>Centers for Disease Control and Prevention, Yaounde, Cameroon

**Background:** In 2019, UNAIDS estimated there were 150,000 new HIV infections among children (<15 years old) and 170,000 among adolescents (10-19 years old), highlighting the ongoing need for HIV testing and diagnosis among these populations. We aim to describe the impact of COVID-19 on HIV testing and diagnosis in children and adolescents.

**Methods:** We analyzed U. S. President's Emergency Plan for AIDS Relief (PEPFAR) Monitoring, Evaluation and Reporting (MER) data from 14 countries in sub-Saharan Africa to compare the number of children (1-14) and older adolescents (15-19) who received an HIV test and were diagnosed as HIV-positive before (January – March, 2020) and during (April – June, 2020) the COVID-19 pandemic across all HIV testing modalities and for index testing (i.e. exposure-based). We calculated the percent change for the two indicators in the two time periods.

**Results:** Overall, pediatric HIV testing and diagnoses declined by 40% and 29%, respectively, across the 14 countries. The testing decline ranged from -13% (DRC) to -81% (Zimbabwe) with the greatest volume of decline in South Africa (-150,469). Lesotho (-61%), Zimbabwe (-57%) and South Africa (-53%) had the largest declines in HIV diagnoses. Pediatric HIV testing and diagnoses increased in Cameroon, 32% and 6%. Pediatric index testing declined by 33% overall with the largest declines in Malawi (-80%) and Lesotho (-66%) and increases in Cameroon (+74%). For older adolescents, HIV testing and diagnoses declined 28% and 29%, respectively, across modalities. Lesotho (-60%), Zimbabwe (-54%) and Ethiopia (-48%) had the largest declines in testing for this group with the greatest volume of decline in South Africa (-147,891). Seven countries had >25% declines in HIV diagnoses for older adolescents, with Lesotho (-50%) and Zimbabwe (-49%) having the largest declines. While index testing for older adolescents decreased in most countries (-31%), it increased in Cameroon (+25%), Nigeria (+20%) and Côte d'Ivoire (+15%).

**Conclusion:** Pediatric and adolescent HIV testing and diagnoses dramatically declined in many sub-Saharan African countries during the COVID-19 pandemic.

Countries – like Cameroon, Côte d'Ivoire and Nigeria – that maintained or increased index testing during COVID-19 had the lowest declines in case finding. To mitigate the effects of COVID-19, programs may consider strategies to maximize index testing for children and adolescents (<19) of people living with HIV.

**Table 1. Changes in HIV Testing and HIV-Positive Results for Children (1-14 years) and Older Adolescents (15-19 years) before (January – March, 2020) and after (April – June, 2020) COVID-19**

|                        | # Pediatric HIV Tests (Apr-Jun 2020) [% Change]* | # Pediatric HIV-positive Results (Apr-Jun 2020) [% Change] | # Pediatric Index Tests (Apr-Jun 2020) [% Change] | # Older Adolescent HIV Tests (Apr-Jun 2020) [% Change] | # Older Adolescent HIV-positive Results (Apr-Jun 2020) [% Change] | # Older Adolescent Index Tests (Apr-Jun 2020) [% Change] |
|------------------------|--|--|---|--|---|--|
| Cameroon               | 29,540 [+32%]                                    | 534 [+46%]   | 9,586 [+74%]                                      | 27,284 [+16%]  | 452 [+29%]  | 961 [+23%]   |
| Côte d'Ivoire          | 26,602 [+17%]                                    | 259 [+14%]   | 8,577 [+9%]                                       | 37,195 [+17%]  | 230 [+2%]   | 1,068 [+15%]   |
| Ethiopia               | 50,760 [-53%]                                    | 278 [-48%]   | 2,925 [-57%]                                      | 54,512 [-48%]  | 194 [-45%]  | 320 [-47%]   |
| Lesotho                | 4,803 [-79%]                                     | 34 [-61%]  | 595 [-66%]  | 9,113 [-60%]   | 126 [-50%]  | 84 [-49%]  |
| Malawi                 | 21,721 [-46%]                                    | 511 [-29%]   | 1,553 [-80%]                                      | 37,601 [-24%]  | 502 [-28%]  | 258 [-79%]   |
| Mozambique             | 125,967 [-37%]                                   | 2,626 [-32%]   | 17,972 [-60]                                      | 163,868 [+28%]   | 3,099 [+27%]  | 1,004 [-63%]   |
| Nigeria                | 83,941 [-19%]                                    | 7,166 [-9%]  | 7,612 [-15%]                                      | 137,956 [-11%]   | 2,379 [+10%]  | 2,492 [+20%]   |
| South Africa           | 168,309 [-40%]                                   | 1,728 [-52%]   | 14,728 [-30%]                                     | 23,263 [-41%]  | 4,161 [-42%]  | 2,224 [-28%]   |
| Uganda                 | 49,060 [-59%]                                    | 981 [-44%]   | 8,691 [-63%]                                      | 174,361 [+24%]   | 2,305 [+23%]  | 2,134 [-62%]   |
| Zimbabwe               | 10,051 [-81%]                                    | 362 [-57%]   | 3,173 [-48%]                                      | 3,273 [-54%]   | 779 [-49%]  | 328 [-64%]   |
| Total (14 Countries)** | 759,011 [-40%]                                   | 15,107 [-29%]  | 136,413 [-33%]                                    | 1,219,072 [-28%]                                       | 19,535 [-29%]   | 21,879 [-31%]  |

**174 DOLUTEGRAVIR-BASED ART IS SUPERIOR TO NNRTI/PI-BASED ART IN CHILDREN AND ADOLESCENTS**

**Anna Turkova, for the ODYSSEY/PENTA-20 Trial Team**  
 MRC Clinical Trial Unit at UCL, London, UK

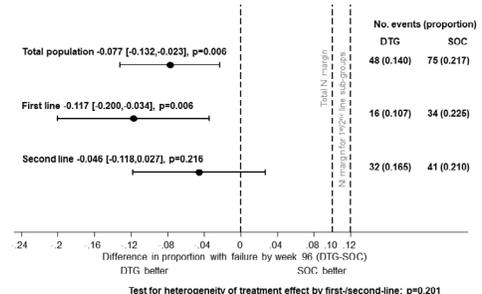
**Background:** ODYSSEY is an international multi-centre randomised non-inferiority trial evaluating dolutegravir (DTG) + 2NRTIs versus standard-of-care (SOC) in children starting first- or second-line ART.

**Methods:** The primary outcome is a Kaplan-Meier estimated proportion of treatment failure defined as confirmed viral load (VL) ≥400c/mL after week 36, lack of virological response by 24 weeks with ART switch, death or new/recurrent WHO4/severe WHO3 event by 96 weeks. Non-inferiority margin is 10% (12% for first-/second-line subgroups).

**Results:** 707 children ≥14kg were randomised (Uganda 47%, Zimbabwe 21%, South Africa 20%, Thailand 9%, Europe 4%); 350 to DTG; 357 to SOC. Median (range) age was 12.2 years (2.9-18); weight 31kg (14-85); 51% male. 311 children started first-line (92% efavirenz among SOC); 396 second-line (72% lopinavir/ritonavir, 25% atazanavir/ritonavir among SOC). Median follow-up was 142 weeks; 687 (97%) reached the primary endpoint or were seen on/after 96 weeks. 48 (14%) DTG vs 75 (22%) SOC had treatment failure by 96 weeks; difference (95% CI) -7.7% (-13.2, -2.3); p=0.006. 40 vs 67 were virological failures and 8 vs 8 were WHO3/4 events/death. Treatment effects were similar in first- and second-line, with no evidence of heterogeneity (p=0.20; fig). 13 (4%) children randomised to DTG changed regimen during follow-up vs 32 (9%) SOC (excluding NRTI changes and changes for growth, simplification, guideline change, stock-out) (p=0.004); 2 vs 21 changes were for treatment failure. At 48 and 96 weeks, proportion with cross-sectional VL<50c/mL and change in CD4 count from baseline were similar between arms. There were 65 SAEs (35 children) in DTG versus 46 (42) in SOC (p=0.45), including 2 vs. 3 deaths; 119 (73 children) grade ≥3 adverse events in DTG vs 135 (88) in SOC (p=0.23). At week 96, mean change in total cholesterol from baseline was -5 mg/dL (95% CI -8,-2) in DTG versus 10 mg/dL (7,13) in SOC (difference (DTG-SOC) -15 (-19,-11); p<0.001). Weight, height and BMI increased marginally more in DTG than SOC (differences (SE) between arms 1kg (0.4), 0.7cm (0.3), 0.3kg/m, (0.1) respectively at 96 weeks).

**Conclusion:** DTG-based ART was superior to SOC based on treatment failure by 96 weeks in children/adolescents starting first- or second-line. There were no safety concerns on DTG. These results support WHO guidelines which recommend DTG-based regimens as preferred ART for children ≥14kg starting first- or second-line ART, allowing harmonisation with adult treatment programmes.

**Fig. Difference in proportion with clinical or virological failure by 96 weeks (DTG-SOC)**



## 175 DoLPHIN2 FINAL RESULTS DOLUTEGRAVIR VS EFAVIRENZ IN LATE PREGNANCY TO 72W POSTPARTUM

**Thokozile R. Malaba**<sup>1</sup>, Irene Nakatudde<sup>2</sup>, Kenneth Kintu<sup>2</sup>, Tao Chen<sup>3</sup>, Sabrina Bakeera-Kitaka<sup>2</sup>, Lucy Read<sup>3</sup>, Helen Reynolds<sup>4</sup>, Angela Colbers<sup>5</sup>, Kelly Byrne<sup>3</sup>, Duolao Wang<sup>3</sup>, Catriona Waitt<sup>4</sup>, Catherine Orrell<sup>1</sup>, Mohammed Lamorde<sup>2</sup>, Landon Myer<sup>1</sup>, Saye Khoo<sup>4</sup>

<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>Makerere University, Kampala, Uganda, <sup>3</sup>Liverpool School of Tropical Medicine, Liverpool, UK, <sup>4</sup>University of Liverpool, Liverpool, UK, <sup>5</sup>Radboud University, Nijmegen, Netherlands

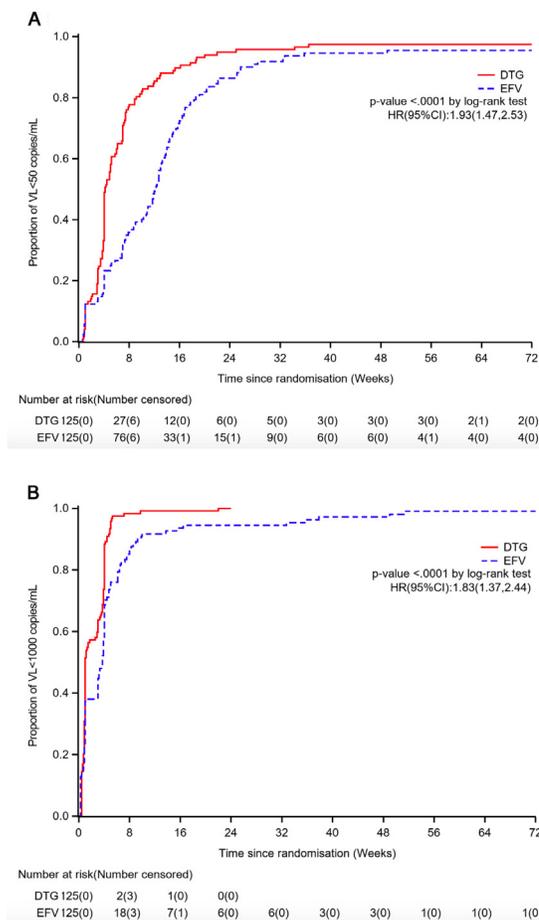
**Background:** Delayed ART initiation in pregnancy is associated with failure to achieve viral suppression and increased risk of MTCT. DoLPHIN-2 (NCT03249181) randomized pregnant women initiating treatment in the third trimester to either dolutegravir (DTG) or efavirenz (EFV) based regimens in South Africa and Uganda. Preliminary analysis of the primary endpoint (viral load (VL) <50 copies at delivery) have been published.

**Methods:** Between Jan-Aug 2018, 268 mothers (safety cohort) were randomized to receive EFV (133) or DTG (135), of whom 250 (EFV-125, DTG-125, intention-to-treat cohort) were evaluable for efficacy. In addition to measurement in pregnancy, VL was also measured at 6, 12, 24, 48 and 72w postpartum (PP). The primary endpoints were VL<50 copies/mL for efficacy; and the occurrence of maternal and/or infant drug related serious adverse events (SAE) for safety. Here we present final data with follow-up of mothers and infants to 72w PP.

**Results:** As previously reported, DTG was associated with superior responses (VL<50) in the first 26w of therapy. At 72w, 116/125 mothers receiving DTG achieved VL<50 with a median time of 4.14 (IQR4.00, 5.14) weeks. In contrast, among 114/125 mothers randomized to the EFV arm, suppression was achieved at a median time of 12.14 (IQR 10.71, 13.29) weeks (adjusted HR 1.93 (95% CI 1.47, 2.53)) (figure). By 72w PP, 21.3% of mothers and 56.2% of infants experienced an SAE, however in mothers only 3% was related to study drug, with no infant drug related events. DTG was well tolerated with a lower frequency of maternal drug related AE (DTG 2.2% vs EFV 3.8%). Overall, the mean change in maternal weight from delivery to 72w PP was -1.2kg, with nonsignificant differences observed by arm in weight retention (DTG -0.7kg vs EFV -1.6kg). No differences in maternal glycosuria or infant hyperglycaemia were observed by arm. Overall 4 infant HIV infections were detected; 3 at delivery in DTG arm, with a new transmission detected at 72w PP in EFV arm despite optimal maternal suppression (VL<50) from delivery and serial negative tests in the child

**Conclusion:** Maternal DTG-based ART was safe and well tolerated. Women randomized to DTG had more rapid viral suppression after initiation of ART and they maintained virologic suppression through the breastfeeding period. The infant HIV infection in the EFV arm highlights the potential for transmission during breastfeeding in mothers despite evidence of virologic suppression.

Figure: Kaplan-Meier plot of time from randomization to viral load (a) <50 and (b) <1000 copies/mL



## 176 ANTEPARTUM WEIGHT GAIN AND ADVERSE PREGNANCY OUTCOMES IN IMPAACT 2010

**Risa M. Hoffman**<sup>1</sup>, Lauren Ziemba<sup>2</sup>, Sean Brummel<sup>2</sup>, Lameck Chinula<sup>3</sup>, Teader G. Nematadzira<sup>4</sup>, Frances Nakayiwa<sup>5</sup>, Jeff Stringer<sup>6</sup>, Chelsea Krotje<sup>7</sup>, Patrick Jean-Philippe<sup>8</sup>, Anne Coletti<sup>9</sup>, Rebecca Zash<sup>10</sup>, Roger Shapiro<sup>10</sup>, Paul Sax<sup>11</sup>, Judith S. Currier<sup>1</sup>, Shahin Lockman<sup>11</sup>

<sup>1</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of North Carolina Project—Malawi, Lilongwe, Malawi, <sup>4</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>5</sup>Makerere University—Johns Hopkins University Research Collaboration, Kampala, Uganda, <sup>6</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>7</sup>Frontier Science Ltd., Inverness-shire, UK, <sup>8</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, <sup>9</sup>FHI 360, Durham, NC, USA, <sup>10</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA, <sup>11</sup>Brigham and Women's Hospital, Boston, MA, USA

**Background:** Insufficient and excess weight gain during pregnancy have been associated with adverse pregnancy outcomes. We evaluated the association between antepartum weight gain and adverse pregnancy outcomes in secondary analyses of IMPAACT 2010 data.

**Methods:** Women with HIV-1 in 9 countries were randomized 1:1:1 at 14-28 weeks gestational age (GA) to start dolutegravir (DTG)+emtricitabine(FTC)/tenofovir alafenamide fumarate (TAF) vs. DTG+FTC/tenofovir disoproxil fumarate(TDF) vs. efavirenz (EFV)/FTC/TDF. By-arm differences in average antepartum weekly weight gain were estimated using generalized estimating equations. Low weight gain was defined as <0.18 kg/week and high weight gain as >0.59 kg/week (Institute of Medicine). Time to event analyses were used to estimate risk of the composite adverse pregnancy outcome of stillbirth (≥20 wks GA), preterm delivery (<37 wks GA) and small for gestational age (SGA: <10th percentile), as well as each of these individual outcomes and neonatal death, using Cox-proportional hazards regression models with weight gain as a time-varying covariate.

**Results:** 643 participants were randomized: 217 in DTG+FTC/TAF, 215 in DTG+FTC/TDF, and 211 in EFV/FTC/TDF arms. Baseline medians were: GA 21.9 weeks, HIV RNA 903 cp/mL, CD4 count 466 cells/uL. The rate of adverse pregnancy outcome was lowest with DTG+FTC/TAF. Weekly average weight gain was highest with DTG+FTC/TAF (0.378kg) compared to DTG+FTC/TDF (0.319kg, p=0.011) and EFV/FTC/TDF (0.291kg, p<0.001). Low weight gain was least common with DTG+FTC/TAF (15.0%) compared with DTG+FTC/TDF (23.6%) or EFV/FTC/TDF (30.0%), with the opposite pattern for high weight gain: DTG+FTC/TAF (12.7%) vs. DTG+FTC/TDF (9.9%) vs. EFV/FTC/TDF (6.3%). Overall, low weight gain was associated with higher risk of any adverse pregnancy outcome (HR 1.4, 95%CI 1.02,1.96) and of SGA (HR 1.5, 95% CI 0.99,2.22). For women in the DTG+FTC/TAF arm, low weight gain was also associated with higher risk of stillbirth (HR 6.2, 95%CI 1.16,32.81) and preterm delivery (HR 3.7, 95%CI 1.14,11.92) compared with normal weight gain. There were no associations between high weight gain and adverse pregnancy outcomes or low or high weight gain and neonatal death.

**Conclusion:** Low (but not high) weight gain was associated with adverse pregnancy outcomes. Women starting DTG+FTC/TAF in pregnancy gained more weight antepartum than women starting DTG+FTC/TDF or EFV/FTC/TDF, while women starting EFV/FTC/TDF had the lowest weight gain.

Table 1: Antepartum weight gain and risk of adverse pregnancy outcomes and neonatal death in IMPAACT 2010

| Outcome                   | Treatment Arm        | Number of Events/Participants | Unadjusted       |                       | Adjusted <sup>1</sup> |                       | P-value: Interaction of Weight and Arm |
|---------------------------|----------------------|-------------------------------|------------------|-----------------------|-----------------------|-----------------------|--|
|                           |                      |                               | Weight Gain      | Hazard Ratio (95% CI) | P-value               | Hazard Ratio (95% CI) |  |
| Stillbirth                | DTG+FTC/TAF<br>N=213 | 31/4                          | Normal           | Ref                   | Ref                   | Ref                   | 0.033                                  |
|                           |                      | 3/2                           | Low              | 4.5 (0.96, 22.9)      | 0.067                 | 6.2 (1.16, 32.8)      |  |
|                           |                      | 0/2                           | High             | 0.0 (0.0, 0.0)        | 0.27                  | 0.3 (0.09, 1.0)       |  |
|                           | DTG+FTC/TDF<br>N=212 | 8/4                           | Normal           | Ref                   | Ref                   | Ref                   |  |
|                           |                      | 1/9                           | Low              | 0.3 (0.06, 2.49)      | 0.81                  | 0.3 (0.09, 2.5)       |  |
|                           |                      | 1/21                          | High             | 0.0 (0.0, 0.2)        | 0.81                  | 0.8 (0.09, 6.1)       |  |
| EFV/FTC/TDF<br>N=207      | 13/8                 | Normal                        | Ref              | Ref                   | Ref                   |                       |  |
|                           | 1/42                 | Low                           | 1.1 (0.10, 12.4) | 0.95                  | 0.9 (0.08, 10.4)      |                       |  |
|                           | 1/13                 | High                          | 3.7 (0.5, 41.1)  | 0.29                  | 8.0 (0.8, 79.8)       |                       |  |
| Preterm Delivery          | DTG+FTC/TAF<br>N=213 | 19/47                         | Normal           | Ref                   | Ref                   | Ref                   | 0.53                                   |
|                           |                      | 1/44                          | Low              | 1.0 (0.2, 2.9)        | 0.92                  | 1.0 (0.36, 2.9)       |  |
|                           |                      | 2/41                          | High             | 0.9 (0.19, 3.7)       | 0.85                  | 0.9 (0.21, 4.2)       |  |
|                           | DTG+FTC/TDF<br>N=212 | 11/8                          | Normal           | Ref                   | Ref                   | Ref                   |  |
|                           |                      | 5/8                           | Low              | 2.9 (0.91, 9.1)       | 0.073                 | 3.7 (1.14, 11.9)      |  |
|                           |                      | 0/2                           | High             | 0.0 (0.0, 0.0)        | 0.28                  | 0.0 (0.0, 0.0)        |  |
| EFV/FTC/TDF<br>N=207      | 14/43                | Normal                        | Ref              | Ref                   | Ref                   |                       |  |
|                           | 2/20                 | Low                           | 0.4 (0.06, 1.9)  | 0.28                  | 0.4 (0.09, 1.8)       |                       |  |
|                           | 1/20                 | High                          | 1.6 (0.12, 4.3)  | 0.98                  | 0.7 (0.15, 3.8)       |                       |  |
| Small for Gestational Age | DTG+FTC/TAF<br>N=213 | 8/76                          | Normal           | Ref                   | Ref                   | Ref                   | 0.17                                   |
|                           |                      | 8/76                          | Low              | 1.5 (0.41, 3.8)       | 0.37                  | 1.1 (0.43, 2.8)       |  |
|                           |                      | 3/20                          | High             | 1.7 (0.47, 6.9)       | 0.42                  | 1.9 (0.54, 7.0)       |  |
|                           | DTG+FTC/TDF<br>N=212 | 11/16                         | Normal           | Ref                   | Ref                   | Ref                   |  |
|                           |                      | 5/20                          | Low              | 1.4 (0.35, 2.9)       | 0.29                  | 1.3 (0.69, 2.3)       |  |
|                           |                      | 5/20                          | High             | 0.9 (0.25, 2.2)       | 0.75                  | 0.9 (0.25, 2.3)       |  |
| EFV/FTC/TDF<br>N=207      | 15/47                | Normal                        | Ref              | Ref                   | Ref                   |                       |  |
|                           | 5/20                 | Low                           | 1.7 (0.47, 6.9)  | 0.42                  | 1.9 (0.54, 7.0)       |                       |  |
|                           | 5/20                 | High                          | 0.9 (0.25, 2.2)  | 0.75                  | 0.9 (0.25, 2.3)       |                       |  |
| Adverse Pregnancy Outcome | DTG+FTC/TAF<br>N=213 | 23/14                         | Normal           | Ref                   | Ref                   | Ref                   | 0.12                                   |
|                           |                      | 6/2                           | Low              | 1.0 (0.12, 2.1)       | 0.97                  | 1.0 (0.12, 2.1)       |  |
|                           |                      | 4/21                          | High             | 0.8 (0.25, 2.4)       | 0.68                  | 0.8 (0.25, 2.4)       |  |
|                           | DTG+FTC/TDF<br>N=212 | 29/14                         | Normal           | Ref                   | Ref                   | Ref                   |  |
|                           |                      | 14/9                          | Low              | 1.9 (0.98, 3.6)       | 0.07                  | 1.1 (0.55, 2.1)       |  |
|                           |                      | 2/9                           | High             | 0.2 (0.01, 2.2)       | 0.38                  | 0.4 (0.09, 1.9)       |  |
| EFV/FTC/TDF<br>N=207      | 24/12                | Normal                        | Ref              | Ref                   | Ref                   |                       |  |
|                           | 1/9                  | Low                           | 1.7 (0.12, 3.0)  | 0.08                  | 1.5 (0.77, 3.1)       |                       |  |
|                           | 1/13                 | High                          | 0.1 (0.06, 0.3)  | 0.41                  | 0.5 (0.07, 4.1)       |                       |  |
| Neonatal Death            | DTG+FTC/TAF<br>N=213 | 16/42                         | Normal           | Ref                   | Ref                   | Ref                   | 0.12                                   |
|                           |                      | 3/44                          | Low              | 1.7 (0.12, 3.0)       | 0.08                  | 1.5 (0.77, 3.1)       |  |
|                           |                      | 1/41                          | High             | 0.1 (0.06, 0.3)       | 0.41                  | 0.5 (0.07, 4.1)       |  |
|                           | DTG+FTC/TDF<br>N=212 | 13/14                         | Normal           | Ref                   | Ref                   | Ref                   |  |
|                           |                      | 3/20                          | Low              | 1.7 (0.12, 3.0)       | 0.08                  | 1.5 (0.77, 3.1)       |  |
|                           |                      | 1/20                          | High             | 0.1 (0.06, 0.3)       | 0.41                  | 0.5 (0.07, 4.1)       |  |
| EFV/FTC/TDF<br>N=207      | 16/42                | Normal                        | Ref              | Ref                   | Ref                   |                       |  |
|                           | 3/44                 | Low                           | 1.7 (0.12, 3.0)  | 0.08                  | 1.5 (0.77, 3.1)       |                       |  |
|                           | 1/41                 | High                          | 0.1 (0.06, 0.3)  | 0.41                  | 0.5 (0.07, 4.1)       |                       |  |

Women were enrolled in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the United States, and Zimbabwe. <sup>1</sup>Adjusted for gestational age status at baseline (14-18 weeks, 19-23 weeks, 24-29 weeks) <sup>2</sup>Adjusted for sex.

Meier method. Efficacy analyses include comparison of maternal HIV RNA <200cp/mL at week 50 PP between the combined DTG arms and EFV arm. **Results:** We randomized 643 women: DTG+FTC/TAF (N=217), DTG+FTC/TDF (N=215), and EFV/FTC/TDF (N=211). Baseline medians: GA 21.9weeks, HIV RNA 903cp/mL, CD4 count 466cells/uL. Six hundred and seven (94.4%) women and 566 (91.7%) of 617 liveborn infants completed the study; 479 (77.6%) infants breastfed (median 49.9 weeks). There were no apparent differences through week 50 PP between arms in the estimated probability of maternal grade≥3 AEs or infant grade≥3 AEs (Table 1). The average change in women's weight from entry through PP was -0.027 kg/week in DTG+FTC/TAF, -0.050 kg/week in DTG+FTC/TDF, and -0.084 kg/week in EFV/FTC/TDF arms. The estimated probability of infant death was higher in the EFV (6.9%) compared to DTG+FTC/TAF (1.0%, p<0.001) and DTG+FTC/TDF (2.0%, p=0.008) arms. Either stillbirth (previously reported) or infant death (combined) occurred as follows: 10 in DTG+FTC/TAF, 15 in DTG+FTC/TDF, and 18 in EFV/FTC/TDF arms. Four infants were diagnosed with HIV: 2 in DTG+FTC/TAF, 1 in DTG+FTC/TDF, and 1 in EFV arm. At 50 weeks PP, proportions of women with HIV RNA <200cp/mL were similar in the combined DTG arms (96.3%) and EFV arm (96.4%). Regimen stops or switches were more frequent in the EFV arm due to virologic failure/drug resistance, and more frequent in the DTG arms due to PP fertility choices. **Conclusion:** At week 50 PP, maternal and infant grade≥3 AEs from enrollment through week 50 PP were similar across arms; infant mortality was higher (though stillbirths somewhat less frequent) in those whose mothers were in the EFV/FTC/TDF arm. Maternal HIV RNA suppression was similarly high in the combined DTG vs the EFV arm, although more women stopped EFV due to virologic failure.

Table 1: IMPAACT 2010 maternal/infant safety outcomes and maternal virologic efficacy outcomes through 50 weeks postpartum

| Safety outcomes <sup>1</sup>   | DTG+FTC/TAF n/N (%)       | DTG+FTC/TDF n/N (%)     | EFV/FTC/TDF n/N (%)          | DTG+FTC/TAF minus DTG+FTC/TDF (95% CI) P-value | DTG+FTC/TDF minus EFV/FTC/TDF (95% CI) P-value | DTG+FTC/TAF minus EFV/FTC/TDF (95% CI) P-value |
|--|---------------------------|-------------------------|------------------------------|--|--|--|
| <b>Maternal outcomes through week 50 postpartum</b>                                      |                           |                         |                              |  |  |  |
| Maternal grade ≥3 adverse event <sup>2,3</sup>   | 53/217 (25.1%)            | 66/215 (30.8%)          | 58/211 (27.9%)               | -5.6% (-14.2%, 2.9%)                           | 2.9% (-5.9%, 11.7%)                            | -2.8% (-11.3%, 5.8%)                           |
| Average (95% CI) weight change per week, entry through postpartum (kg/week) <sup>4</sup> | -0.027 (-0.042, -0.012)   | -0.050 (-0.066, -0.034) | -0.084 (-0.098, -0.070)      | 0.023 (0.001, 0.045)                           | 0.034 (0.013, 0.055)                           | 0.057 (0.036, 0.078)                           |
| Obese <sup>5</sup> at week 50 (n/N)  | 43/190 (22.6%)            | 35/190 (18.4%)          | 29/193 (15.0%)               |  |  |  |
| Estimated creatinine clearance <sup>6</sup> week 50 (mean (SD) mL/min)                   | 124 (42)                  | 138 (35)                | 131 (36)                     |  |  |  |
| <b>Infant outcomes through week 50 after birth</b>                                       |                           |                         |                              |  |  |  |
| Infant grade ≥3 adverse event <sup>2,4</sup>   | 51/208 (25.3%)            | 53/202 (28.0%)          | 63/207 (30.9%)               | -3.2% (-12.8%, 6.3%)                           | -2.3% (-12.1%, 7.5%)                           | -5.5% (-14.3%, 3.2%)                           |
| Infant deaths <sup>2,5</sup>   | 2/208 (1.0%)              | 4/202 (2.0%)            | 14/207 (6.9%)                | -1% (-3.4%, 1.3%)                              | -4.9% (-8.9%, -0.9%)                           | -3.9% (-9.7%, 2.2%)                            |
| Stillbirth <sup>2</sup>  | 8/216 (3.7%)              | 11/213 (5.2%)           | 4/211 (1.9%)                 | -1.5% (-5.4%, 2.4%)                            | 3.3% (-0.2%, 6.8%)                             | 1.8% (-1.3%, 4.9%)                             |
| Infant HIV infection <sup>2,6</sup>  | 2/208 (0.98%)             | 1/202 (0.50%)           | 1/207 (0.55%)                | 0.5% (-1.2%, 2.1%)                             | -0.1% (-1.5%, 1.4%)                            | 0.4% (-1.3%, 2.2%)                             |
| Major congenital anomaly <sup>7</sup>  | 3/208 (1%)                | 0                       | 2/207 (1%)                   |  |  |  |
| <b>Maternal virologic efficacy outcomes and regimen switches</b>                         |                           |                         |                              |  |  |  |
|  | Combined DTG Arms n/N (%) | EFV/FTC/TDF n/N (%)     | Difference (95% CI), p-value |  |  |  |
| Week 50 HIV-1 RNA <200 cp/mL <sup>8</sup>  | 366/380 (96.3%)           | 386/393 (98.4%)         | -0.1% (-3.3%, 3.2%), 0.97    |  |  |  |
| <b>Virologic failure<sup>9</sup></b>   |                           |                         |                              |  |  |  |
| DTG+FTC/TAF  | 13/217 (5.1%)             | DTG+FTC/TDF             | 12/215 (5.6%)                | EFV/FTC/TDF                                    | 24/211 (11.4%)                                 |  |
| Stopped or switched study ART early for any reason                                       |                           |                         |                              |  |  |  |
|  | 33                        | 25                      | 26                           |  |  |  |
| Virologic failure/resistance   |                           |                         |                              |  |  |  |
|  | 0                         | 0                       | 14                           |  |  |  |
| Adverse event  |                           |                         |                              |  |  |  |
|  | 4                         | 7                       | 3                            |  |  |  |
| PP fertility choices   |                           |                         |                              |  |  |  |
|  | 11                        | 10                      | 0                            |  |  |  |
| Other <sup>10</sup>  |                           |                         |                              |  |  |  |
|  | 18                        | 13                      | 8                            |  |  |  |

<sup>1</sup>The safety outcome measure: at least one grade≥3 adverse event from randomization through 50 weeks postpartum. <sup>2</sup>Pairwise p-value for the difference in proportions based on a Kaplan Meier curve between the two indicated treatment groups. <sup>3</sup>Renal and estimating equation models. <sup>4</sup>BM23/kg/m<sup>2</sup>. <sup>5</sup>Creatinine clearance was calculated using Cockcroft-Gault formula. <sup>6</sup>The safety outcome measure: at least one grade≥3 adverse event through 50 weeks after birth. <sup>7</sup>Post hoc two-sample test of the difference in binomial proportions. <sup>8</sup>Analysis groups were defined based on randomization (1:1) with analyses conducted among participants with available data. <sup>9</sup>Maternal HIV RNA at 50 weeks postpartum. <sup>10</sup>Virologic failure defined as 2 successive HIV-1 RNA tests >200 cp/mL at or after 24 weeks on study. <sup>11</sup>Other: most frequent with frequent contact, relocated, non-compliance. <sup>12</sup>14 infants with HIV breastfed and received ARV prophylaxis. <sup>13</sup>1 had first positive test within 14 days after birth (one with highest maternal through delivery HIV RNA=42cp/mL), 1 had positive test at 6 weeks (HIV RNA=10 starting 8 weeks on study), and one at 60 weeks after birth (EFV arm, maternal VL=0 through 26 weeks PP). <sup>14</sup>15/202 infant deaths occurred within 28 days after birth. <sup>15</sup>The major congenital anomalies were atrial septal defect (1), talipes equinovarus (1), duodenal atresia and ileal stenosis (1) and subgaleal cyst (1).

177 SAFETY/EFFICACY OF DTG VS EFV, TDF VS TAF IN PREGNANCY/POSTPARTUM: IMPAACT 2010 TRIAL



Lameck Chinula<sup>1</sup>, Sean Brummel<sup>2</sup>, Lauren Ziembra<sup>3</sup>, Katie McCarthy<sup>3</sup>, Benjamin Johnson<sup>4</sup>, Nahida Chakhtoura<sup>5</sup>, Patrick Jean-Philippe<sup>6</sup>, Lynda Stranix-Chibanda<sup>7</sup>, Violet Korutaru<sup>8</sup>, Hasena Cassim<sup>9</sup>, Fairlie Lee<sup>10</sup>, Gaerolwe Masheto<sup>11</sup>, Paul Sax<sup>12</sup>, Judith S. Currier<sup>13</sup>, Shahin Lockman<sup>12</sup>

<sup>1</sup>University of North Carolina Project—Malawi, Lilongwe, Malawi, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>FHI 360, Durham, NC, USA, <sup>4</sup>Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, <sup>5</sup>National Institute of Child Health and Human Development, Bethesda, MD, USA, <sup>6</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, <sup>7</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>8</sup>Baylor College of Medicine Children's Foundation, Kampala, Uganda, <sup>9</sup>Soweto IMPAACT CRS, Johannesburg, South Africa, <sup>10</sup>Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, <sup>11</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>12</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>13</sup>University of California Los Angeles, Los Angeles, CA, USA

**Background:** We previously reported safety and virologic efficacy of dolutegravir (DTG)+emtricitabine (FTC)/tenofovir alafenamide fumarate (TAF) vs DTG+FTC/tenofovir disoproxil fumarate (TDF) vs efavirenz (EFV)/FTC/TDF through delivery. We now present results from enrollment through week 50 postpartum (PP).

**Methods:** Pregnant women with HIV-1 in 9 countries were randomized 1:1:1 to start open-label DTG+FTC/TAF, DTG+FTC/TDF, or EFV/FTC/TDF at 14-28 weeks gestational age (GA). Safety outcomes included pairwise regimen comparisons of grade≥3 maternal and infant adverse events (AEs, primary), infant mortality, and infant HIV infection. Safety probabilities were estimated with the Kaplan-

178 ADVERSE PREGNANCY OUTCOMES AMONG HIV-INFECTED WOMEN EXPOSED TO ISONIAZID IN BRIEF-TB

Amita Gupta<sup>1</sup>, Michael Hughes<sup>2</sup>, Jorge T. Leon-Cruz<sup>2</sup>, Anchalee Avihingsanon<sup>3</sup>, Noluthando Mwelase<sup>4</sup>, Patrice Severe<sup>5</sup>, Ayotunde Omoz-Oarhe<sup>6</sup>, Gaerolwe Masheto<sup>6</sup>, Laura Moran<sup>7</sup>, Constance A. Benson<sup>8</sup>, Richard E. Chaisson<sup>9</sup>, Susan Swindells<sup>10</sup>, for the ACTG 5279 BRIEF TB Trial

<sup>1</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Thai Red Cross AIDS Research Center, Bangkok, Thailand, <sup>4</sup>Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, <sup>5</sup>GHEKIO, Port-au-Prince, Haiti, <sup>6</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>7</sup>Social & Scientific Systems, Silver Spring, MD, USA, <sup>8</sup>University of California San Diego, San Diego, CA, USA, <sup>9</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>10</sup>University of Nebraska Medical Center, Omaha, NE, USA

**Background:** Isoniazid (INH) preventive therapy (IPT), a key strategy for reducing tuberculosis (TB) and death among persons with HIV (PWH), was associated with increased composite adverse pregnancy outcomes in IMPAACT P1078 trial. The BRIEF-TB trial demonstrated non-inferiority of one-month of isoniazid and rifapentine versus nine months of IPT. We assessed adverse pregnancy outcomes among women exposed to IPT in a secondary analysis.

**Methods:** BRIEF-TB enrolled 3,000 adults with HIV infection in 10 countries. Pregnancy was an exclusion criterion at entry. We analyzed adverse pregnancy outcomes (non-live births; a composite of still-births, spontaneous abortions, ectopic pregnancy; preterm; low birthweight) among women who became pregnant in the IPT arm, according to whether the first pregnancy during follow-up started during INH use (INH-exposed) or after IPT was finished (INH-unexposed). Logistic regression models were used to evaluate association of pregnancy outcome with INH exposure adjusting for age, CD4, antiretroviral therapy (ART) and latent TB infection (LTBI) status at study entry, and separately for these variables at or proximal to pregnancy outcome.

**Results:** Of 1,614 women participants, 812 were randomized to IPT, 136 of whom became pregnant; 128 of 136 had pregnancy outcome data available. At entry, median age was 29 years, median CD4 was 534 cells/mm<sup>3</sup>, 45 (35%) were on ART (EFV or NVP-based regimen), and 26 (20%) were LTBI-positive. There were 93 live births and 35 non-live births (including 6 elective abortions). Sixteen (41%) of 39 INH-exposed pregnancies had non-live births (including 3 elective abortions) compared to 19 (21%) of 89 INH-unexposed pregnancies (including 3 elective abortions). A composite adverse pregnancy outcome was observed in 13 (33%) of 39 INH-exposed versus 16 (18%) of 89 INH-unexposed. The odds ratio, adjusted for covariates at or proximal to pregnancy outcome, of non-live birth for INH-exposed versus INH-unexposed was 1.87 (95% CI 0.75-4.69) and of adverse pregnancy outcome was 1.73 (95% CI 0.67-4.50; Table).

**Conclusion:** INH exposure starting in the first trimester was associated with increased adverse pregnancy outcomes in this trial. While none of the associations reached statistical significance in analyses adjusted for covariates at or proximal to delivery, this finding supports other recent data from the TEMPRANO and P1078 trials.

Table. Adverse pregnancy outcomes among HIV-infected pregnant women exposed versus not exposed to isoniazid (INH) preventive therapy in the BRIEF-TB ACTG 5279 trial

|  | INH-exposed during pregnancy N=39 | INH-unexposed during pregnancy N=89 | Unadjusted OR (95% CI) | OR adjusted for covariates at study entry <sup>a</sup> (95% CI) | OR adjusted for covariates proximal to pregnancy outcome <sup>b</sup> (95% CI) |
|--|-----------------------------------|-------------------------------------|------------------------|---|--|
| <b>Live Birth</b>                                |                                   |                                     |                        |   |  |
| Yes  | 23 (59%)                          | 70 (79%)                            |                        |   |  |
| No   | 16 (41%)                          | 19 (21%)                            | 2.56 (1.13, 5.79)      | 2.97 (1.26, 7.02)   | 1.87 (0.75, 4.69)  |
| <b>Spontaneous abortion &lt;20 wks</b>           |                                   |                                     |                        |   |  |
| Yes  | 12 (31%)                          | 13 (15%)                            |                        |   |  |
| No   | 3 (8%)                            | 3 (3%)                              |                        |   |  |
| <b>Ectopic pregnancy</b>                         |                                   |                                     |                        |   |  |
| Yes  | 0 (0%)                            | 2 (2%)                              |                        |   |  |
| No   | 1 (3%)                            | 1 (1%)                              |                        |   |  |
| <b>Composite Adverse Pregnancy Event</b>         |                                   |                                     |                        |   |  |
| Yes  | 13 (33%)                          | 16 (18%)                            | 2.28 (0.97, 5.38)      | 2.63 (1.06, 6.53)   | 1.73 (0.67, 4.50)  |
| No   | 26 (67%)                          | 73 (82%)                            |                        |   |  |
| <b>Low Birthweight &lt;2.5kg in live births</b>  |                                   |                                     |                        |   |  |
| Yes  | 3 (14%)                           | 7 (13%)                             | 1.02 (0.24, 4.35)      | Not obtained <sup>d</sup>                                       | Not obtained <sup>d</sup>  |
| No   | 19 (86%)                          | 45 (87%)                            |                        |   |  |
| Missing  | 1                                 | 18                                  |                        |   |  |
| <b>Preterm Birth &lt;37 weeks in live births</b> |                                   |                                     |                        |   |  |
| Yes  | 4 (20%)                           | 11 (23%)                            | 0.84 (0.23, 3.04)      | Not obtained <sup>d</sup>                                       | Not obtained <sup>d</sup>  |
| No   | 16 (80%)                          | 37 (77%)                            |                        |   |  |
| Missing  | 3                                 | 22                                  |                        |   |  |

## 179 PrEP USE DURING ACUTE HIV INFECTION IN A COMMUNITY SETTING COMPROMISES HIV DIAGNOSIS

**Donn J. Colby**<sup>1</sup>, Suteeraporn Pinyakorn<sup>1</sup>, Ratchapong Kanaprach<sup>2</sup>, Sasiwimol Ubolyam<sup>3</sup>, Tippawan Pankam<sup>3</sup>, Kultida Poltavee<sup>2</sup>, Eugene Kroon<sup>2</sup>, Carlo Sacdalan<sup>2</sup>, Nitiya Chomchey<sup>2</sup>, Jintanat Ananworanich<sup>4</sup>, Siriwat Akapirat<sup>5</sup>, Sandhya Vasani<sup>1</sup>, Nittaya Phanuphak<sup>2</sup>, Mark de Souza<sup>2</sup>, for the RV254/SEARCH010 Research Group  
<sup>1</sup>US Military HIV Research Program, Bethesda, MD, USA, <sup>2</sup>Institute of HIV Research and Innovation, Bangkok, Thailand, <sup>3</sup>Thai Red Cross AIDS Research Centre, Bangkok, Thailand, <sup>4</sup>University of Amsterdam, Amsterdam, Netherlands, <sup>5</sup>Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand

**Background:** The inadvertent use of antiretroviral (ARV) drugs for pre-exposure prophylaxis (PrEP) during the window period of acute HIV infection (AHI) may delay seroconversion on HIV diagnostic tests. We report on the HIV serological response in a community cohort of men who have sex with men (MSM) who were exposed to PrEP during AHI.

**Methods:** Participants with AHI were enrolled in the RV254/SEARCH 010 cohort in Bangkok, Thailand. HIV serology, including 4th generation (G) (Architect HIV Ag/Ab Combo or Alinity I HIV Ag/Ab Combo), 3rdG (Genscreen HIV-1/2 v2), 2ndG (Avioq) and Western blot (WB, Genetic Systems HIV-1), was performed at baseline, 24 and 48 weeks.

**Results:** Six participants were exposed to PrEP (daily tenofovir disoproxil fumarate/emtricitabine) during AHI, with a median PrEP duration of 11 days (range 2-91 days). All initiated PrEP after a nonreactive 3rdG or 4thG screening test. HIV diagnosis was by HIV RNA screening of pooled pre-PrEP specimens (4/6 with a range of 2-15 days) or by reactive 3rd/4thG test at a follow-up PrEP

visit (2/6, range 29-91 days). All had confirmed plasma HIV RNA on pre-PrEP specimens (table). Participants were switched immediately at diagnosis from PrEP to dolutegravir-based antiretroviral therapy (ART) with ≥3 drugs and all maintained VL<20 copies/mL from 4 weeks. Reactive serology at ART start (week 0) was 0/6 4thG, 3/6 3rdG, and 1/6 2ndG, and at 24 weeks was 1/6 4thG, 4/6 3rdG, 4/6 2ndG. One subsequent seroconversion of a 4thG test occurred at 48 weeks. Only 2 participants, exposed to PrEP for 15 and 29 days, seroconverted to all three assays at week 48. One participant remained nonreactive to all 3 tests at 48 weeks; he was exposed to PrEP for 2 days and had a maximum of VL 276 copies/mL at baseline. All WB results were indeterminate at week 24.

**Conclusion:** PrEP use during AHI, with immediate switch to ART, was associated with delay or failure to seroconvert over 48 weeks in this Thai cohort. The 3rdG test was most sensitive at all time points, but was reactive in only 4/6 participants by 48 weeks. Least sensitive was the 4thG test, with seroconversion in only 2/6 of participants, and in no case did the WB fully evolve. Standard HIV testing algorithms are not sensitive to the muted serologic response observed in the presence of ARV drugs. Other testing methods, using nucleic acid platforms or alternate serologic tests, may be necessary to diagnose HIV infection in these cases.

Table: Clinical and diagnostic test results from 6 Thai MSM who started PrEP during acute HIV infection. xG=x generation HIV antibody test, □=nonreactive, ■=reactive, ND=not done

| Participant | Pre-PrEP VL (cps/mL) | # days on PrEP | Pre-ART VL (cps/mL) | Pre-ART CD4(cells/μL) | Week 0 |    |    | Week 24 |    |    | Week 48 |    |    |    |
|-------------|----------------------|----------------|---------------------|-----------------------|--------|----|----|---------|----|----|---------|----|----|----|
|             |                      |                |                     |                       | 2G     | 3G | 4G | 2G      | 3G | 4G | 2G      | 3G | 4G |    |
| 3145        | 16,780               | 7              | 216                 | 685                   | □      | ■  | □  | ■       | □  | □  | ND      | □  | □  | □  |
| 4634        | 219                  | 2              | 2,317               | 528                   | □      | □  | □  | □       | ■  | □  | □       | ND | □  | □  |
| 5803        | 58                   | 29             | 37,222              | 302                   | □      | ■  | □  | □       | ■  | □  | □       | ND | ND | ■  |
| 6313        | 223,361              | 91             | 389                 | 690                   | ■      | ■  | □  | ■       | ■  | □  | ND      | ND | ND | □  |
| 6934        | 32                   | 2              | 276                 | 739                   | □      | □  | □  | □       | □  | □  | □       | □  | □  | □  |
| 7167        | 317                  | 15             | 8,802               | 521                   | □      | □  | □  | ■       | ■  | ■  | ND      | ND | ND | ND |

## 180 A CLUSTER-RANDOMIZED TRIAL OF TRADITIONAL HEALERS DELIVERING HIV TESTING IN UGANDA

**Radhika Sundararajan**<sup>1</sup>, Juliet Mwanga-Amumpaire<sup>2</sup>, Matthew Ponticello<sup>3</sup>, Myung Hee Lee<sup>1</sup>, Steffanie Strathdee<sup>4</sup>, Winnie Muyindike<sup>5</sup>, Denis Nansera<sup>5</sup>, Rachel King<sup>6</sup>, Daniel Fitzgerald<sup>1</sup>

<sup>1</sup>Weill Cornell Medicine, New York, NY, USA, <sup>2</sup>Mbarara University of Science and Technology, Mbarara, Uganda, <sup>3</sup>Cornell University, Ithaca, NY, USA, <sup>4</sup>University of California San Diego, San Diego, CA, USA, <sup>5</sup>Immune Suppression Syndrome Clinic, Mbarara Regional Referral Hospital, Mbarara, Uganda, <sup>6</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** HIV counseling and testing is an essential component of controlling the HIV/AIDS epidemic. However, uptake of HIV testing is sub-optimal in sub-Saharan Africa. For example, in rural Uganda, only 39% of sexually active adults have received an HIV test within the last 12 months. In Uganda, and throughout sub-Saharan Africa, traditional healers are ubiquitous, informal providers who are frequently preferred for healthcare services, and are more accessible than biomedical clinics. We hypothesized that involving traditional healers in HIV testing may increase uptake in a rural, endemic region.

**Methods:** We conducted a cluster randomized trial of an HIV testing program to determine the effectiveness of traditional healers delivering HIV testing to directly to adults receiving care at their practices. The unit of randomization in this trial was the traditional healer site as a cluster. Outcomes were assessed at the level of the individual client of participating healers. Traditional healers and their clients in Mbarara Township were randomized to an intervention group or standard of care (control). Intervention arm healers delivered point-of-care oral swab HIV tests to sexually active adult clients who reported no HIV testing within the prior 12 months. Control arm healers provided referral for HIV testing at nearby medical clinics. Primary outcome for this trial was individual clients receiving an HIV test within 90 days of their visit. Secondary outcomes were new HIV diagnosis and linkage to care for those newly diagnosed.

**Results:** Between August 2019 and February 2020, 17 traditional healers were randomized (9 intervention, 8 control) and 500 clients of unknown HIV serostatus (250 per arm) enrolled. In the intervention arm, 250 participants (100%) received an HIV test compared with 57 (22.8%) in the control arm, a 77.2% increase in HIV testing uptake (95% CI 72.8 – 81.6%, p<0.001, Figure 1). Ten participants in the intervention arm (4%) tested HIV-positive, compared with zero cases in the control arm (p=0.002). Seven of the newly diagnosed

patients report linkage to HIV care within 90-days of study enrollment, compared with none in the control arm (p=0.015).

**Conclusion:** Delivery of point-of-care HIV tests by traditional healers to adults of unknown serostatus significantly increased the rate of HIV testing, diagnosis, and linkage to care in rural Uganda. This novel, community-based approach holds promise for increasing uptake of HIV testing in Sub-Saharan Africa.

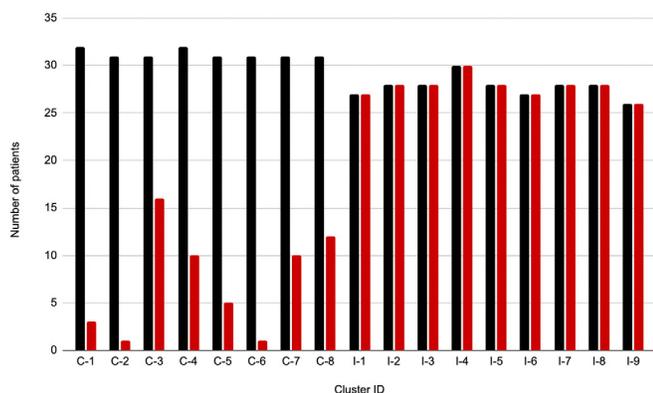


Figure 1. Numbers of individual participants enrolled (black) and those who received an HIV test (red) at each cluster location. Cluster ID numbers 1 through 8 on the left of the graph reflect control arm sites. Clusters ID numbers 1 through 9 on the right of the graph are intervention arm sites.

**181 HIV SELF-TESTING TO OPTIMIZE FACILITY TESTING: A CLUSTER-RANDOMIZED TRIAL IN MALAWI**

**Kathryn Dovel<sup>1</sup>, Sundeep Gupta<sup>1</sup>, Christian Stillson<sup>2</sup>, Misheck Mphande<sup>3</sup>, Kelvin Balakasi<sup>3</sup>, Isabella Robson<sup>3</sup>, Chi-Hong Tseng<sup>1</sup>, Alemayehu Amberbir<sup>1</sup>, Leslie Berman<sup>2</sup>, Shaikat Khan Khan<sup>2</sup>, Joep J. Van Oosterhout<sup>1</sup>, Naoko Doi<sup>2</sup>, Brooke Nichols<sup>4</sup>**

<sup>1</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>2</sup>Clinton Health Access Initiative, Boston, MA, USA, <sup>3</sup>Partners in Hope, Lilongwe, Malawi, <sup>4</sup>Boston University, Boston, MA, USA

**Background:** High coverage of HIV testing among outpatients in generalized epidemics is critical for sustained epidemic control; however, severe human resource and infrastructure constraints have made this impractical in LMICs. HIV self-testing (HIVST) distributed at outpatient departments is a promising solution, but little is known about how to best implement the strategy.

**Methods:** A cluster randomized implementation trial was conducted at 9 facilities in Malawi between February–April, 2020. Facilities were randomized 1:1:1: PITC (provider-initiated one-on-one testing); Passive HIVST (group Oraquick<sup>®</sup> demonstration and outpatient/guardian-initiated HIVST distribution); and Active HIVST (group Oraquick<sup>®</sup> demonstration, provider-initiated one-on-one HIVST distribution). All activities took place prior to routine consultations and were implemented by cadres with no more than a secondary school certificate. The primary outcome was self-reported same-day HIV-testing among eligible (never tested positive and never tested or last tested >12 months ago) adults, using a difference-in-differences analysis (2-weeks pre and 3-weeks post intervention). Exit surveys were conducted with a systematically sampled subset of adult outpatients and guardians. Healthcare worker time was observed by study staff.

**Results:** 3,182 adults were enrolled (1851 outpatients, 1331 guardians): 33% were male and 38% were eligible for HIV testing (Table). HIV testing among eligible individuals was low across arms, with highest coverage in Active HIVST post-intervention (26%). There was a 13 percentage-point increase (95%CI: 4.2–22.8%) in testing between Active HIVST compared to PITC post-intervention, but no significant difference between Passive HIVST and PITC. Increased coverage was mainly among adult guardians. Active HIVST had the highest positivity (8/101, 8%, 95%CI: 2.3–13.2%), with 7/8 (88%, 95%CI: 47–99%) reporting same-day ART initiation. Total provider time required per test completed was estimated to increase 8% post-intervention in PITC, and decrease by 36% and 53% in Passive and Active HIVST, respectively.

**Conclusion:** Facility HIVST in outpatient departments implemented by lower-level cadres can increase testing coverage and both testing and health worker efficiency within routine settings.

Table. Participant characteristics and outcomes across the arms of a HIVST implementation science trial targeting adult outpatients and outpatient guardians (N = 3,182)

|   | PITC        |              |                         | Passive HIVST |              |                         | Active HIVST |              |                         | 95% CI (Active HIVST - Δ PITC) | 95% CI (Active HIVST - Δ PITC) |
|---|-------------|--------------|-------------------------|---------------|--------------|-------------------------|--------------|--------------|-------------------------|--------------------------------|--------------------------------|
|   | pre (n=207) | post (n=202) | Difference (Δ pre-post) | pre (n=256)   | post (n=244) | Difference (Δ pre-post) | pre (n=415)  | post (n=449) | Difference (Δ pre-post) |                                |                                |
| <b>Demographic variables</b>                                  |             |              |                         |               |              |                         |              |              |                         |                                |                                |
| Male  | 148 (71%)   | 272 (41%)    | -                       | 96 (37%)      | 251 (39%)    | -                       | 139 (33%)    | 174 (39%)    | -                       | -                              | -                              |
| Eligible for testing (never tested and tested >12mo ago)      | 168 (81%)   | 244 (37%)    | -                       | 107 (42%)     | 224 (38%)    | -                       | 195 (47%)    | 274 (61%)    | -                       | -                              | -                              |
| <b>Study outcomes</b>   |             |              |                         |               |              |                         |              |              |                         |                                |                                |
| Same-day HIV testing  | 39 (19%)    | 71 (11%)     | 2%                      | 23 (9%)       | 54 (8%)      | 2%                      | 22 (5%)      | 101 (23%)    | 10%                     | -8.30%                         | 8%                             |
| Among those in need of testing*, same-day testing             | 17168 (10%) | 18204 (10%)  | 5%                      | 9707 (9%)     | 11224 (14%)  | 5%                      | 13135 (7%)   | 19274 (24%)  | 15%                     | -8.20%                         | 13%                            |
| New HIV-positive  | 159 (2.56%) | 271 (2.82%)  | -                       | 123 (4.35%)   | 254 (3.7%)   | -                       | 102 (8%)     | 810 (1.83%)  | -                       | -                              | -                              |
| Among new positives, same-day ART initiation                  | 1/1 (100%)  | 2/2 (100%)   | -                       | 1/1 (100%)    | 2/2 (100%)   | -                       | 0/0          | 7/8 (88%)    | -                       | -                              | -                              |
| Total health care worker time** per test completed (minutes)  | 36          | 39           | 4 (8%)                  | 49            | 44           | -25 (49%)               | 54           | 25           | -29 (53%)               | 28                             | 33                             |
| Active health care worker time** per test completed (minutes) | 16          | 19           | 3 (19%)                 | 36            | 25           | -11 (30%)               | 29           | 13           | -16 (55%)               | 14                             | 19                             |

\* Difference in difference  
 \*\* In need of testing is defined as never tested HIV positive and tested >12 months ago  
 † Defined as all HIV Diagnostic Assistant and Expert Clinician time spent in outpatient or outpatient specific PITC departments, including time spent actively engaging clients or guardians, waiting for clients to arrive, completing paper work, and time in clinic when the study team was unable to determine what activity was being done.  
 ‡ Defined as active HIV Diagnostic Assistant and Expert Clinician time spent engaging clients or guardians, this includes health talks, HIVST demonstrations, mobilizing individuals for testing, HIVST distribution or testing, and pre- and post-test counselling.  
 § Time measured in first test completed in the national testing algorithm. Second and confirmatory test not included in time calculation.

**182 COMMUNITY MULTIMONTH ART PROVISION: POOLED ANALYSIS OF 2 CLUSTER-RANDOMIZED TRIALS**

**Geoffrey Fatti<sup>1</sup>, John Lopes<sup>2</sup>, Nicoletta Mabheha-Ngorima<sup>1</sup>, Apollinaire Tiam<sup>3</sup>, Betty Tukei<sup>4</sup>, Pedro Pisa<sup>5</sup>, Vincent Tukei<sup>6</sup>, Khotso Maile<sup>6</sup>, Charles Chasela<sup>5</sup>, Ashraf Grimwood<sup>1</sup>**

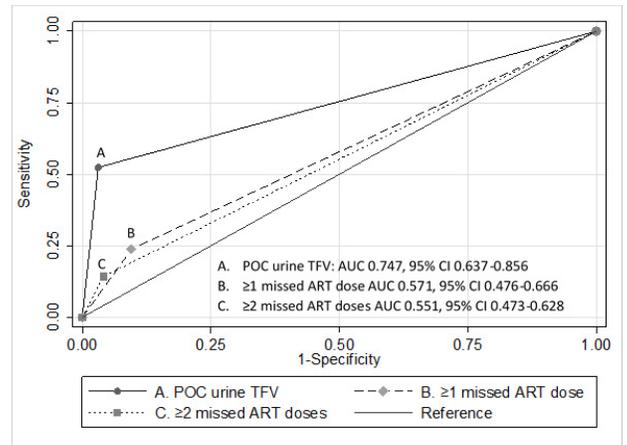
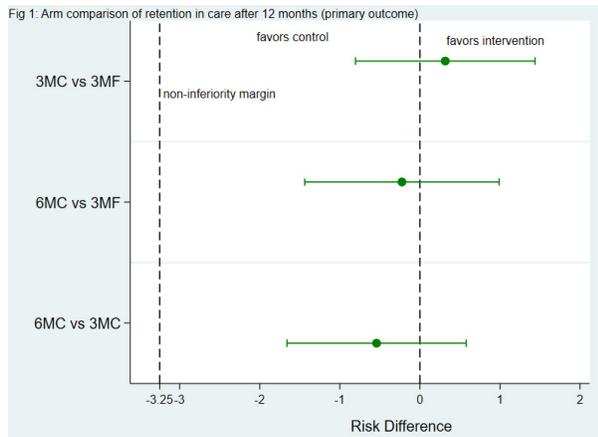
<sup>1</sup>Kheth'Impilo AIDS Free Living, Cape Town, South Africa, <sup>2</sup>Stellenbosch University, Cape Town, South Africa, <sup>3</sup>Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, <sup>4</sup>Equip Health, Maseru, Lesotho, <sup>5</sup>Right to Care, Johannesburg, South Africa, <sup>6</sup>Elizabeth Glaser Pediatric AIDS Foundation, Maseru, Lesotho

**Background:** Differentiated service delivery (DSD) models provide flexibility for patients accessing antiretroviral treatment (ART) in sub-Saharan Africa, and decongest health facilities. With the global COVID-19 pandemic, DSD models, which promote social distancing and facilitate easier access to ART in the community are critical. We investigated the clinical effectiveness of community-based multimonth ART provision in high HIV prevalence settings in Zimbabwe and Lesotho.

**Methods:** Individual-level patient data were pooled from two cluster-randomized noninferiority trials that compared 3 and 6-monthly community-based ART provision vs. standard of care facility-based ART dispensing for stable HIV patients, which were conducted between 2017–2019. Both trials had three-arms: ART collected 3-monthly at facilities (3MF, control); ART provided 3-monthly in community ART refill groups (CARGs) (3MC); and ART provided 6-monthly in either CARGs or at community-distribution points (6MC). Stable adults with viral suppression receiving ART ≥6 months were recruited. The primary outcome was retention in ART care 12 months after enrolment, and secondary outcomes were viral suppression and number of unscheduled clinic visits between months 0–12. Individual-level regression analyses were conducted by intention-to-treat specifying for clustering and adjusted for country.

**Results:** 60 randomized clusters were included with 3817, 2893 and 3426 participants enrolled in arms 3MF, 3MC and 6MC, respectively. After 12 months, retention in 3MF, 3MC and 6MC was 95.0%, 95.7% and 95.1%, respectively; adjusted risk differences 0.3 (95% CI: -0.8 to 1.4); -0.2 (95% CI: -1.4 to 1.0) and -0.5 (95% CI: -1.7 to 0.6) for 3MC vs. 3MF, 6MC vs 3MF, and 6MC vs 3MC, respectively (Figure 1). All comparisons achieved the prespecified non-inferiority margin of -3.25%. Viral suppression after 12 months was high in all arms; 97.8%, 98.6% and 97.9% in 3MF, 3MC and 6MC, respectively, adjusted risk ratios=1.0 (95% CI: 0.99–1.01); 1.0 (0.97–1.01) and 1.0 (0.97–1.01) for 3MC vs. 3MF, 6MC vs 3MF, and 6MC vs 3MC, respectively. No differences in the number of unscheduled clinic visits between arms were apparent.

**Conclusion:** Community-based ART provision at both 3 and 6-monthly intervals were noninferior vs. 3-monthly facility-based dispensing in high HIV-prevalence settings for stable HIV patients. These DSD models are now more critical than ever, and can be scaled-up to promote social distancing and clinic decongestion to mitigate the impact of COVID-19.



**183 POINT-OF-CARE URINE TENOFOVIR VERSUS SELF-REPORTED ART ADHERENCE IN ROUTINE HIV CARE**

**Tamsin K. Phillips<sup>1</sup>**, Yolanda Gomba<sup>1</sup>, David Huang<sup>2</sup>, Landon Myer<sup>1</sup>  
<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>Western Cape Provincial Department of Health, Cape Town, South Africa

**Background:** The Abbott point-of-care (POC) urine lateral flow assay for tenofovir (TFV) was developed and validated on stored specimens from patients on pre-exposure prophylaxis. We compared the POC urine TFV test to self-reported ART adherence among patients in routine HIV care in Cape Town, South Africa.

**Methods:** Adults living with HIV, on a TFV-containing regimen and having a routine viral load (VL) test at a large ART clinic were enrolled in a cross-sectional study. Interviews collected demographic information and self-reported missed ART doses in the past 7 days. A urine sample was collected and immediately tested using the POC urine TFV test. VL results from the day of visit were abstracted from medical records.

**Results:** 314 patients were enrolled Feb-Nov 2020 (mean age 39 years, 79% female, 61% >5 years on ART). Most patients were on EFV+FTC/3TC+TFV. Only 20 patients (6%) had no urine TFV detected. VL was <50 and <1000 copies/mL in 259 (82%) and 293 (93%) patients, respectively. Among 55 patients with VL ≥50, 13 had no urine TFV detected (sensitivity 24%, 95% CI 13-37). Among 259 patients with VL <50, 252 had urine TFV detected (specificity 97%, 95% CI 95-99). Using a threshold of 1000 copies/mL, there was higher sensitivity (n=21 with VL ≥1000: sensitivity 52%, 95% CI 30-74), but similar specificity (n=293 with VL <1000: specificity 97%, 95% CI 94-99). Results were independent of patient sex and weight. Self-reported adherence was high. Only 11% of patients (33/314) reported ≥1 missed ART dose in the past 7 days; 5% (15/314) reported missing ≥2 doses. Compared to self-report, the POC urine TFV test had a higher sensitivity, specificity and area under the receiver operating curve (ROC) to predict VL ≥50 and VL ≥1000, although confidence intervals were overlapping (Figure). Among 21 patients with VL ≥1000 copies/mL, 10 (48%) had urine TFV detected and 16 (76%) reported no missed doses in the past 7 days.

**Conclusion:** In this largely adherent cohort, TFV detected on the POC urine test identified almost all suppressed patients and was a better predictor of VL than self-report. Although sensitivity was low, this simple POC test could prompt adherence discussions with patients with no TFV detected. There may also be value in combining this objective adherence measure with VL test results to flag patients with raised VL in the presence of ART. Further research is needed to understand the practical applications of this POC test for patient care, particularly in non-adherent populations.

**184 RAPID VS SAME-DAY TREATMENT INITIATION FOR PATIENTS WITH TB SYMPTOMS AT HIV DIAGNOSIS**

**Nancy Dorvil<sup>1</sup>**, Cynthia Riviere<sup>1</sup>, Patrice Severe<sup>1</sup>, Heejung Bang<sup>2</sup>, Jessy Devieux<sup>3</sup>, Kerlyne Lavoile<sup>1</sup>, Stephanie Bousleiman<sup>4</sup>, Etienne Cremieux<sup>1</sup>, Emelyne Dumont<sup>1</sup>, Alexandra Apollon<sup>1</sup>, Benedict Charles<sup>1</sup>, Giovanni Sainly<sup>1</sup>, Mikerlyne Faustine<sup>1</sup>, Jean W. Pape<sup>1</sup>, Serena Koenig<sup>5</sup>

<sup>1</sup>GHEKIO, Port-au-Prince, Haiti, <sup>2</sup>University of California Davis, Davis, CA, USA, <sup>3</sup>Florida International University, Miami, FL, USA, <sup>4</sup>Harvard Medical School, Boston, MA, USA, <sup>5</sup>Brigham and Women's Hospital, Boston, MA, USA

**Background:** Delays in ART initiation for TB testing are associated with high rates of loss to follow-up. There are limited data on outcomes with same-day testing and treatment for patients with TB symptoms at HIV diagnosis.

**Methods:** We conducted a randomized trial comparing same-day and rapid (7 days) TB testing and treatment initiation among adult patients with TB symptoms at HIV diagnosis at GHEKIO in Haiti. The same-day group received Xpert Ultra results and initiated either TB medication or ART on the day of HIV diagnosis. The rapid group received Ultra results within the first week and started ART on Day 7 if not diagnosed with TB. Dolutegravir (DTG) replaced efavirenz (EFV) as the first-line anchor drug in December 2018. The primary outcome was 48-week HIV-1 RNA <200 copies/mL.

**Results:** Between November 2017 and December 2019, 500 participants were randomized to rapid (n=250) or same-day treatment (n=250) (Table 1). 234 (46.8%) were female, median age was 37 (IQR: 30, 45), and median CD4 count was 278 (134, 421). In the rapid group, 40/41 (97.6%) participants diagnosed with TB started TB drugs; 244 (97.6%) started ART. In the same-day group, 45/45 (100%) diagnosed with TB started TB drugs; 250 (99.6%) started ART. There were no statistically significant differences in 48-week outcomes between groups. In the rapid group, 224/250 (89.6%) were retained in care, and of these, 171 (76.3%) had HIV-1 RNA <200 copies/mL. In the same-day group, 219/250 (87.6%) were retained in care, and of these, 155 (70.8%) had HIV-1 RNA <200 copies/mL. The primary outcome (48-week HIV-1 RNA <200 copies/mL) was achieved by 171/250 (68.4%) in the rapid group and 155/250 (62.0%) in the same-day group (p=0.133). Outcomes were superior among participants who initiated ART with DTG instead of EFV, with HIV-1 RNA <200 copies/mL in 82.4% vs. 68.1%, respectively, (p=0.001) among those receiving viral load testing, and 75.3% vs. 60.4% among those randomized (p<0.001).

**Conclusion:** Among patients with TB symptoms at HIV diagnosis, both rapid and same-day treatment are associated with near-universal initiation of TB treatment and ART, with no significant difference in 48-week outcomes. Viral suppression rates were lower than anticipated, which we attribute to high rates of transmitted EFV resistance, political instability with a national lockdown, and the SARS-CoV-2 outbreak in Haiti during the study period. Viral suppression rates are superior with DTG, supporting the rapid transition from EFV to DTG-based ART.

**Table 1: Forty-Eight Week Outcomes for Participants in the Rapid and Same-Day Groups and for Initiation of DTG vs. EFV Regimen**

|                      | Rapid (n=250)   | Same-Day (n=250) | p-value | Initiated EFV (n=308) | Initiated DTG (n=186) | p-value |
|----------------------|-----------------|------------------|---------|-----------------------|-----------------------|---------|
| Lost to follow-up    | 21/250 (8.4%)   | 21/250 (8.4%)    | 1.000   | 25/308 (8.1%)         | 12/186 (6.5%)         | 0.496   |
| Died                 | 5/250 (2.0%)    | 10/250 (4.0%)    | 0.190   | 10/308 (3.2%)         | 4/186 (2.2%)          | 0.477   |
| Retained in Care (%) | 224/250 (89.6%) | 219/250 (87.6%)  | 0.482   | 273/308 (88.6%)       | 170/186 (91.4%)       | 0.328   |
| HIV-1 <200 copies/mL | 171/224 (76.3%) | 155/219 (70.8%)  | 0.184   | 186/273 (68.1%)       | 140/170 (82.4%)       | 0.001*  |

\*from chi square tests for binary variables

**185 COMMUNITY DISTRIBUTION OF ART DURING CIVIL UNREST AND COVID-19 IN HAITI**

**Patrice Joseph<sup>1</sup>**, Hoi Ching Cheung<sup>2</sup>, Neil Sequeria<sup>2</sup>, Jean Edouard Mathon<sup>1</sup>, Marc-Antoine Jean-Juste<sup>1</sup>, Youry Macius<sup>1</sup>, Rode Secours<sup>1</sup>, Colette Guiteau<sup>1</sup>, Karine Severe<sup>1</sup>, Nancy Dorvil<sup>1</sup>, Eli Maxime Francois<sup>1</sup>, Adias Marcelin<sup>1</sup>, Rose-Irene Verdier<sup>1</sup>, Marie Marcelle Deschamps<sup>1</sup>, Jean W. Pape<sup>1</sup>

<sup>1</sup>GHESKIO, Port-au-Prince, Haiti; <sup>2</sup>Analysis Group, Inc, Boston, MA, USA

**Background:** Challenges to retain patients with HIV in Haiti were worsened by civil unrest and the COVID-19 pandemic. To support patient retention, GHESKIO, one of the largest HIV care centers in the Caribbean, set up 11 community distribution points (CDPs) for antiretroviral therapy (ART) pickup and viral load testing at satellite sites in Port-au-Prince neighborhoods, and offered home delivery to patients.

**Methods:** The choice to pick up ART at CDPs was offered to all patients by 5/2019. Nurses at CDPs referred patients to GHESKIO clinics if they were symptomatic or due for physician visit. Data on all ART pickups in 5/1/2019-10/23/2020 from GHESKIO's electronic health records were described. Multivariable logistic regressions were used to identify patient characteristics associated with having ≥1 non-clinic visit (i.e. at CDP or home).

**Results:** 16,234 patients completed ≥1 drug pickup visits during the study period (41.2% male; mean±SD age 41.8±13.3 years; 14% newly initiated ART since 5/2019; 6.0±4.1 years since ART enrollment as of 5/2019 among previously enrolled patients). 39.3% of patients had ≥1 non-clinic pickup (31.8% had ≥1 CDP visit, 12.7% had ≥1 home visit). Patients attended 77,514 visits (4.8±2.2 per patient), 16.2% and 3.3% of which were CDP and home visits, respectively. Since 9/2019, when nationwide lockdown due to political unrest began, 21.9% of visits were at CDPs and 3.9% at home. After 3/2020, when the first COVID-19 case was detected in Haiti, 15,183 patients completed 35,564 visits (2.3±1.2 visits per patient); proportions of visits at CDPs and home increased to 27.5% and 4.7%, respectively. Of patients with visits since 3/2020, 2,824 (18.6%) patients relied solely on non-clinic ART pickups (13.7% only at CDPs; 3.3% only at home). Regression suggests male sex, higher education, higher income, age <18 years, longer time since ART initiation, and non-single civil status were associated with having ≥1 non-clinic visit. Patients living in Carrefour, a neighborhood blocked from GHESKIO clinics during civil unrest, were more likely to have ≥1 non-clinic visit than patients from other neighborhoods.

**Conclusion:** Community distribution of ART builds resilience in health systems and supports continuity of care when access to clinics is limited. These services may be especially preferred by younger patients with longer time since ART initiation, higher income and education, and living in areas with limited access to medical clinics.

| Logistic Regression Results                          | ≥1 Non-clinic Visits<br>N=16,234 |              |         |
|--|----------------------------------|--------------|---------|
|  | OR                               | 95% CI       | P-value |
| <b>Independent Variable</b>                          |                                  |              |         |
| Enrolled on ART after May 2019                       | 0.40                             | (0.32, 0.50) | <0.001* |
| ≥6 months on ART by May 2019                         | 1.70                             | (1.41, 2.05) | <0.001* |
| Male sex   | 1.10                             | (1.02, 1.18) | 0.010*  |
| <b>Age (Reference: ≥40 years)</b>                    |                                  |              |         |
| 0 to 18 years  | 1.61                             | (1.32, 1.95) | <0.001* |
| 19 to 40 years                                       | 0.97                             | (0.90, 1.05) | 0.435   |
| <b>Income (Reference: None)</b>                      |                                  |              |         |
| Less than \$150/year                                 | 0.31                             | (0.25, 0.40) | <0.001* |
| \$150 - \$1,000/year                                 | 0.85                             | (0.76, 0.94) | 0.002*  |
| \$1,001 - \$5,000/year                               | 1.17                             | (1.07, 1.29) | <0.001* |
| \$5,001 - \$10,000/year                              | 1.35                             | (1.21, 1.52) | <0.001* |
| \$10,001 - \$20,000/year                             | 1.28                             | (1.06, 1.55) | 0.009*  |
| Above \$20,000/year                                  | 1.07                             | (0.77, 1.48) | 0.683   |
| Unknown  | 1.05                             | (0.59, 1.89) | 0.866   |
| <b>Education (Reference: None or Preschool only)</b> |                                  |              |         |
| Primary  | 1.18                             | (1.06, 1.30) | 0.001*  |
| Secondary  | 1.40                             | (1.27, 1.54) | <0.001* |
| University/Professional                              | 1.31                             | (1.09, 1.57) | 0.004*  |
| Unknown  | 1.17                             | (0.71, 1.93) | 0.532   |
| <b>Civil Status (Reference: Single)</b>              |                                  |              |         |
| Divorced, Separated or Widowed                       | 1.26                             | (1.12, 1.40) | <0.001* |
| Married or Cohabiting                                | 1.11                             | (1.01, 1.21) | 0.022*  |
| Unknown  | 2.03                             | (1.05, 3.95) | 0.036*  |
| <b>Residence Area (Reference: Carrefour)</b>         |                                  |              |         |
| Delmas   | 0.78                             | (0.71, 0.87) | <0.001* |
| Pétion-Ville   | 0.65                             | (0.57, 0.75) | <0.001* |
| Plaine   | 0.44                             | (0.40, 0.49) | <0.001* |
| Port-Au-Price  | 0.74                             | (0.67, 0.81) | <0.001* |
| Other  | 0.19                             | (0.17, 0.21) | <0.001* |

**186 RESILIENCE OF HIV ACTIVITIES DURING COVID-19 PANDEMIC AT HEALTH FACILITIES IN AFRICA**



**Tiffany G. Harris<sup>1</sup>**, Edward G. Jaszi<sup>1</sup>, Carlos G. Laudari<sup>2</sup>, Bonaparte Nijirazana<sup>1</sup>, Hermann Brou<sup>3</sup>, Faustin Malele<sup>4</sup>, Ruben G. Sahabo<sup>5</sup>, Zenebe Melaku<sup>6</sup>, Mark Hawken<sup>7</sup>, Mirriah Vitale<sup>8</sup>, Florence Bayoa<sup>9</sup>, Prisca Kasonde<sup>10</sup>, Wafaa M. El-Sadr<sup>1</sup>

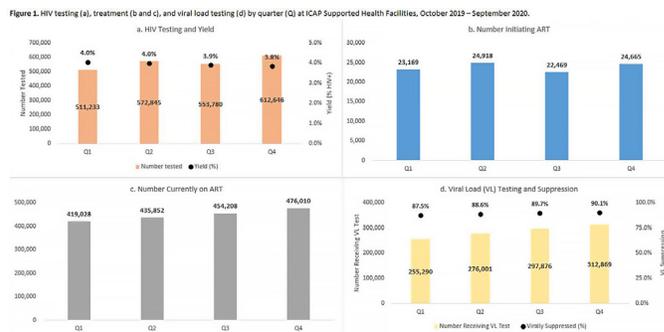
<sup>1</sup>ICAP at Columbia University, New York, NY, USA; <sup>2</sup>ICAP at Columbia University, Luanda, Angola; <sup>3</sup>ICAP at Columbia University, Abidjan, Cote d'Ivoire; <sup>4</sup>ICAP at Columbia University, Kinshasa, Congo; <sup>5</sup>ICAP at Columbia University, Mbabane, Swaziland; <sup>6</sup>ICAP at Columbia University, Addis Ababa, Ethiopia; <sup>7</sup>ICAP at Columbia University, Kisumu, Kenya; <sup>8</sup>ICAP at Columbia University, Maputo City, Mozambique; <sup>9</sup>ICAP at Columbia University, Juba, South Sudan; <sup>10</sup>ICAP at Columbia University, Lusaka, Zambia

**Background:** The COVID-19 pandemic has impacted healthcare access due to travel restrictions, fear of exposure at health facilities (HF), changes in national policies and redirection of resources. We aimed to examine the impact that COVID-19 had on specific HIV activities including HIV testing, antiretroviral therapy (ART) initiation and viral load (VL) testing and suppression (VLS) at President's Emergency Plan for AIDS Relief (PEPFAR)-supported HF in 11 African countries.

**Methods:** Retrospective routine data collected quarterly (Q) [Q1:October-December 2019; Q2:January-March 2020; Q3:April-June 2020; Q4:July-September 2020] from 1059 ICAP-supported HF in Angola (HF=17), Burundi (HF=88), Cameroon (HF=73), Cote d'Ivoire (HF=145), the Democratic Republic of Congo (HF=199), Eswatini (HF=42), Ethiopia (HF=31), Kenya (HF=1), Mozambique (HF=59), South Sudan (HF=20) and Zambia (HF=384) were analyzed to determine quarterly trends along the HIV testing and treatment cascade.

**Results:** Overall, there was a 3.3% decrease in the number HIV tested from Q2 (572,845) to Q3 (553,780) (Figure 1). This change varied by country ranging from a 57% decrease in Kenya (5,460 to 2,364) to a 104% increase in Cameroon (45,940 to 93,735). The number testing HIV-positive in all countries declined by 5.0% from Q2 (22,662) to Q3 (21,553) with little change in yield (4.0% vs. 3.9%). In Q4 the number HIV tested increased by 10.6% (to 612,646) from Q3, and the number testing HIV+ increased by 9.0% (23,457) with little change in yield (3.8%). New ART initiations declined by 9.8% from Q2 to Q3 but increased again by 9.8% in Q4 (Q2:24,918; Q3:22,469; Q4:24,665). In every quarter, the number of patients currently on ART increased—Q1:419,028; Q2:435,852; Q3:454,208 and Q4:476,010. The number receiving a VL test also increased (Q1:255,290; Q2:276,001; Q3:297,876; Q4:312,869) with slight increases in the percentage with VLS (Q1:87.5%; Q2:88.6%; Q3:89.7%; Q4:90.1%).

**Conclusion:** In this large study, with the of COVID-19 pandemic acceleration from Q2 to Q3, the number HIV tested decreased along with declines in number of HIV+ persons identified and new ART initiations. However, rebound was brisk as the pandemic progressed (Q4), demonstrating remarkable HIV program resilience. The number on ART, VL testing and VLS continued to increase throughout the period. This may have been, in part, due to recent expansions of non-HF-based differentiated service delivery models that include more diverse groups.



# SCIENCE SPOTLIGHTS™

## 187 HOST-PATHOGEN INTERACTIONS OF HIGHLY PATHOGENIC CORONAVIRUSES REVEAL DRUG TARGETS

**David E. Gordon**<sup>1</sup>, Mehdi Bouhaddou<sup>1</sup>, Veronica V. Rezelj<sup>2</sup>, Kris M. White<sup>3</sup>, Matthew J. O'Meara<sup>4</sup>, Gwendolyn M. Jang<sup>1</sup>, Jeffrey Z. Guo<sup>1</sup>, Joseph M. Hiatt<sup>1</sup>, Kirsten Obernier<sup>1</sup>, Pedro Beltrao<sup>5</sup>, Marco Vignuzzi<sup>2</sup>, Adolfo Garcia-Sastre<sup>3</sup>, Kevan M. Shokat<sup>1</sup>, Brian K. Shoichet<sup>1</sup>, Nevan J. Krogan<sup>1</sup>, for the QBI-Coronavirus Research Group

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>Institut Pasteur, Paris, France, <sup>3</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>4</sup>University of Michigan, Ann Arbor, MI, USA, <sup>5</sup>EMBL-EBI, Hinxton, UK

**Background:** The novel coronavirus SARS-CoV-2, the causative agent of COVID-19, has caused worldwide social and economic disruption. Initial efforts to treat SARS-CoV-2 were hampered by limited knowledge of the molecular details of SARS-CoV-2 infection. To identify molecular targets for SARS-CoV-2 therapeutics, we mapped the host-pathogen protein interactions of SARS-CoV-2, and investigated host dependency pathways that are required for SARS-CoV-2 infection using drug, knockdown and knockout screens. Concerns regarding the mutagenic potential of SARS-CoV-2 also led us to inquire whether a conserved set of human host factors may be required for infection by all highly pathogenic coronaviruses, thus representing pan-coronavirus drug targets. Therefore, we also mapped the host protein interactions of SARS-CoV-1 and MERS-CoV.

**Methods:** We cloned, tagged and expressed proteins encoded by SARS-CoV-2, SARS-CoV-1, and MERS-CoV in HEK-293T cells, which are permissive to infection by all three viruses. Cells expressing individual proteins were harvested, affinity purifications performed in 96-well format, and protein mass spectrometry was utilized to identify physical interaction partners of each viral protein. Drug treatments, RNAi knockdowns and CRISPR/Cas9 knockouts were tested for SARS-CoV-2 viral phenotypes in Vero, Caco2 or A549-ACE2 cells.

**Results:** We report 389 high-confidence interactors of SARS-CoV-2, 366 interactions for SARS-CoV-1, and 296 interactions for MERS-CoV. Among the SARS-CoV-2 interactors, we identified at least 66 druggable human proteins or host factors, and screening small molecules targeting these pathways using multiple viral assays have identified at least four sets of pharmacological agents that demonstrate antiviral activity against SARS-CoV-2. Comparison of the host-pathogen interactomes of SARS-CoV-2 with the other highly pathogenic coronaviruses SARS-CoV-1 and MERS highlights shared host interactions which may represent pan-coronavirus drug targets.

**Conclusion:** We successfully utilized systematic protein interaction mapping to identify drug targets for SARS-CoV-2, leading to several COVID-19 clinical studies investigating the efficacy of drugs perturbing these pathways. Furthermore, comparative proteomics of the related coronaviruses SARS-CoV-1 and MERS-CoV identified shared host interactions which may represent pan-coronavirus drug targets. For a full list of contributing authors see: Gordon, D. E. et al. *Nature* 583, 459–468 (2020); Gordon, D. E. et al. *Science* 370 (2020).

## 188 SYSTEMATIC ANALYSIS OF SARS-CoV-2 INFECTION OF AN ACE2-NEGATIVE HUMAN AIRWAY CELL

**Maritza N. Puray-Chavez**<sup>1</sup>, Kyle M. LaPak<sup>1</sup>, Travis P. Schrank<sup>2</sup>, Jennifer L. Elliott<sup>1</sup>, Dhaval P. Bhatt<sup>1</sup>, Megan J. Agajanian<sup>1</sup>, Ria Jasuja<sup>1</sup>, Dana Q. Lawson<sup>1</sup>, D. Neil Hayes<sup>3</sup>, Sean P. Whelan<sup>1</sup>, Amjad Horani<sup>1</sup>, Steven L. Brody<sup>1</sup>, Dennis J. Goldfarb<sup>1</sup>, M. Ben Major<sup>1</sup>, Sebla B. Kutluay<sup>1</sup>

<sup>1</sup>Washington University in St Louis, St Louis, MO, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>University of Tennessee, Memphis, TN, USA

**Background:** Established in vitro models for SARS-CoV-2 infection are limited and include cell lines of non-human origin and those engineered to overexpress ACE2, the cognate host cell receptor. Although Calu-3, a human lung cell line which endogenously expresses ACE2, supports SARS-CoV-2 replication, they are significantly less permissive to infection than other models. Furthermore, ACE2 expression in the respiratory tract is low and emerging evidence suggests the utilization of alternative host cell receptors and attachment factors may compensate for low ACE2 expression levels in the lung. We identified human

H522 lung adenocarcinoma cells as naturally permissive to SARS-CoV-2 infection despite complete absence of ACE2.

**Methods:** A panel of 10 cell lines, with variable expression levels of ACE2 and TMPRSS2 were infected with SARS-CoV-2 strain 2019-nCoV/USA-WA1/2020. Viral replication was monitored through assessment of cell-associated and cell-free viral RNA (vRNA) by QRT-PCR as well as N staining by FACS and in situ hybridization. Effect of blocking S protein by neutralizing antibodies and an ACE2-Fc decoy peptide, ACE2 blocking by a specific antibody, and ACE2 knockout by CRISPR on SARS-CoV-2 replication was determined by Q-RT-PCR for vRNAs. Various viral entry inhibitors were used to pathway of SARS-CoV-2 entry in H522 cells. RNA sequencing and proteomics was used to study the cell and innate immune responses in infected H522 cells. siRNA-mediated knockdown was utilized to further characterize the pathway of immune sensing.

**Results:** Infection of H522 cells required the SARS-CoV-2 spike protein, though in contrast to ACE2-dependent models, spike alone was not sufficient for H522 infection. Temporally resolved transcriptomic and proteomic profiling revealed alterations in cell cycle and the antiviral host cell response, including MDA5-dependent activation of type-I interferon signaling. Focused chemical screens point to important roles for clathrin-mediated endocytosis and endosomal cathepsins in SARS-CoV-2 infection of H522 cells.

**Conclusion:** These findings imply the utilization of an alternative SARS-CoV-2 host cell receptor which may impact tropism of SARS-CoV-2 and consequently human disease pathogenesis.

## 189 SARS-CoV-2 SPIKE PROTEIN INDUCES MONOCYTE APOPTOSIS AND INTERLEUKIN-8 PRODUCTION

**Aswath Padmanabhan Chandrasekar**<sup>1</sup>, Mark Maynes<sup>1</sup>, Sekar Natesampillai<sup>1</sup>, F.N.U. Shweta<sup>1</sup>, Andrew D. Badley<sup>1</sup>, Nathan W. Cummins<sup>1</sup>

<sup>1</sup>Mayo Clinic, Rochester, MN, USA

**Background:** In the setting of SARS-CoV-2 infection and COVID-19 illness, a subset of symptomatic patients has been reported to experience severe leukopenia. Viral proteins have been described to have the capacity to induce cell death in peripheral blood cells in infections such as HIV. Given the expression of the cognate receptor, ACE-2, on the surface of Peripheral blood mononuclear cells (PBMCs), we hypothesized that SARS-CoV-2 may induce leukopenia via spike protein ligand-receptor interaction.

**Methods:** PBMCs were isolated from the fresh blood of normal donors and were treated with 1ug/ml of recombinant spike protein, and analyzed for cell death via the Incucyte Live/Cell imaging system. To measure subset specific cell death, PBMCs treated with recombinant spike protein for 48 hours were analyzed by flow cytometry for the expression of cell specific surface receptors and concomitant active caspase 3 expression. Culture supernatant was analyzed by multiplex cytokine analysis to evaluate the presence of pro-inflammatory cytokines. Similar assays were carried out in the presence of a spike-binding domain-antagonistic antibody in order to determine the specific role of spike-ACE2 interaction in causing cell death. Finally, cells from COVID positive patients were analyzed to determine if similar results were observable in-vivo.

**Results:** The treatment of PBMCs with recombinant SARS-CoV-2 spike resulted in significant cell death over time in 2 out of three donors tested (p<0.05) by IncuCyte live imaging analysis. When analyzed for subset specific cell death, a significant increase in cell death (p<0.01), as measured by Caspase 3, was observed in CD14+CD3- cells, correlating with the monocyte population. Supernatants from these cultures demonstrated markedly increased IL-8 production (p=0.0536). Cultures carried out in the presence of a spike antagonistic antibody abrogated the effects of spike protein, indicating a direct relationship between spike-ACE2 interaction and cell death in this sub-population. Similar flow cytometric analysis from 5 febrile patients with COVID-19 demonstrated significantly increased monocyte apoptosis (p<0.05), compared to CD3+ lymphocytes from the same donors; whereas significantly increased monocyte apoptosis was not observed in 5 afebrile COVID-19 patients.

**Conclusion:** These results indicate that SARS-CoV-2 spike protein may induce apoptosis specifically in Monocytes, in an ACE2 dependent manner, in some but not all patients.

## 190 LUCIFERASE COMPLEMENTATION ASSAY FOR IDENTIFICATION OF SARS-CoV-2 3CLPRO INHIBITORS

Jonathan Rawson<sup>1</sup>, Alice Duchon<sup>1</sup>, Olga Nikolaitchik<sup>1</sup>, Vinay K. Pathak<sup>1</sup>, Wei-Shau Hu<sup>1</sup>

<sup>1</sup>National Cancer Institute, Frederick, MD, USA

**Background:** The 3C-like protease (3CLpro) of SARS-CoV-2 has been widely pursued as a target for COVID-19 anti-viral drug development because it is essential for viral replication and lacks significant homology to human proteases. However, drug development for 3CLpro has been hindered by a lack of cell-based reporter assays that can be performed in a BSL-2 setting. Current efforts to identify 3CLpro inhibitors largely rely upon in vitro screening, which fails to account for the cell permeability and cytotoxicity of compounds, or assays involving replication-competent virus, which must be performed in a BSL-3 facility and are not amenable to high-throughput screening.

**Methods:** To address these limitations, we explored the use of a cell-based luciferase complementation reporter to identify inhibitors of SARS-CoV-2 3CLpro in a BSL-2 setting. We constructed lentiviral vectors that co-express 3CLpro and a split reporter in which two luciferase fragments were linked by a 3CLpro cleavage site. 3CLpro-mediated cleavage of the reporter was expected to result in loss of complementation and low luciferase activity, whereas inhibition of 3CLpro was expected to result in significantly higher levels of luciferase activity.

**Results:** In the absence of inhibitors, we found that most of the luciferase reporter was cleaved by 3CLpro, resulting in low luciferase activity. However, inhibition of 3CLpro, either with the small molecule GC376 or an inactivating mutation (C145A), prevented cleavage and resulted in an ~10-fold increase in luciferase reporter activity. We also found that our reporter assay can easily distinguish between cytotoxicity and true inhibition of 3CLpro. With this assay, we screened 31 additional small molecules for activity against SARS-CoV-2 3CLpro, including HIV protease inhibitors, HCV protease inhibitors, and various other compounds that have been reported to inhibit 3CLpro. Of these, only four compounds exhibited significant activity against SARS-CoV-2 3CLpro in cells: boceprevir, Z-FA-FMK, calpain inhibitor XII, and GRL-0496.

**Conclusion:** We have developed a novel luciferase complementation reporter assay for identification of SARS-CoV-2 3CLpro inhibitors in living cells. The assay is sensitive, rapid, easy to perform, and can readily differentiate cytotoxicity from 3CLpro inhibition, a powerful feature that should reduce false positives during screening. This assay should greatly facilitate efforts to identify more potent inhibitors of SARS-CoV-2 3CLpro.

## 191 EXCESS OF SARS-CoV-2 SUBGENOMIC RNAs IN CELLS AND FLUIDS DURING ACUTE INFECTION

Sushama Telwate<sup>1</sup>, Holly A. Martin<sup>1</sup>, Joseph K. Wong<sup>2</sup>, Chuanyi M. Lu<sup>2</sup>, Sulgji A. Lee<sup>3</sup>, Steven A. Yuki<sup>2</sup>

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>San Francisco VA Medical Center, San Francisco, CA, USA, <sup>3</sup>San Francisco General Hospital, San Francisco, CA, USA

**Background:** SARS-CoV-2 is transcribed as genomic RNA (gRNA) and different subgenomic RNAs (sgRNA), allowing variation in viral gene expression. However, the extent and clinical significance of subgenomic transcription remain unknown. We hypothesized that SARS-CoV-2 RNA levels would vary between genome regions and between patients, tissues, and sample types (cells or fluids).

**Methods:** We designed and validated 7 novel RT-ddPCR assays that target the 5' and 3' untranslated regions (UTR), non-structural genes found only in full length gRNA [Main Proteinase (NSP5) and RNA dependent RNA polymerase (RdRp)], and 3' structural genes [Spike (S), membrane (M), and nucleocapsid (N)] that are also contained in different sgRNAs. Assay efficiencies were measured on standards derived from plasmids and viral stock supernatants. Levels of all 7 RNA regions were measured in nucleic acid extracted by the Abbott m<sub>2</sub>000 platform from nasopharyngeal (NP) swabs from 3 SARS-CoV-2 infected individuals, and in cells and supernatant from NP, oropharynx (OP), and saliva isolated from 3 additional individuals.

**Results:** In all samples, levels of 3' targets (M, N, and 3'UTR) tended to be higher than 5' targets (5' UTR, NSP5, and RdRp), suggesting an excess of 3' sgRNAs (3'UTR/5'UTR=2.4-6.2 and nucleocapsid/RdRp=1.1-7.5 for NP samples; n=6,

p=0.03). All SARS-CoV-2 RNAs were detected in both cells and supernatant from NP, OP, and saliva, but tended to be higher in the NP than OP. In saliva but not NP or OP, levels of gRNA/ $\mu$ L sample were consistently higher in the cells compared to supernatant (cell/sup=2.7-44.8). Surprisingly, the excess of 3' over 5' viral RNAs was even greater in the supernatant (3'UTR/5'UTR=8.2-38.7) compared to cells (3'UTR/5'UTR=1.5-6.2) from NP, OP, and saliva (p=0.016 across all), suggesting a greater excess of sgRNAs in the cell-free fluids.

**Conclusion:** The higher levels of 3' targets suggest an excess of sgRNA in all samples. Assays that target 3' regions found in sgRNAs (N, 3'UTR) may be more sensitive for detecting SARS-CoV-2, but may not indicate infectious virus. The greater excess of 3' transcripts in cell-free fluids suggests that sgRNAs are released from cells and/or persist to a greater degree than gRNAs. Future studies should investigate how levels of sgRNA change over the course of infection in cells and cell-free fluids, and whether sgRNA levels correlate with measures of disease transmission or severity.

## 192 IDENTIFICATION OF A NEW LENTIVIRUS RESTRICTION COUNTERACTED BY VPR



Rodrigo Matus Nicodemos<sup>1</sup>, David R. Ambrozak<sup>1</sup>, Sam Darko<sup>1</sup>, Amy Ransier<sup>1</sup>, Daniel C. Douek<sup>1</sup>, Richard A. Koup<sup>1</sup>

<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

**Background:** Lentiviruses encode non-structural accessory proteins that function to counteract host restriction factors. The lentivirus protein Vpr is known to block G2 to M transition of the cell cycle and degrades various host DNA repair proteins, including Uracil-N-Glycosylases: UNG2 and SMUG1. The reason why Vpr induces these cellular changes in the infected cell is unknown.

**Methods:** We explored this question by direct infection of primary resting and activated CD4 T cells with a CCR5-tropic replication-competent GFP reporter virus. We measured GFP expression by flow cytometry and virus expression by ELISA. We also performed bulk and scRNAseq of sorted GFP+ cells to measure host mRNAs and virus mRNAs. Additionally, we used a Uracil-qPCR to quantify provirus uracil versus thymidine incorporation. Lastly, we stimulated CellTrace labelled infected resting cells with and without Vpr and measured cellular proliferation in the constant presence of ART.

**Results:** We detected resting GFP+ cells 3 to 4 days after infection.

Transcriptome analysis of resting GFP+ versus activated GFP+ revealed a pathway for dNTP production in resting CD4 T cells where deoxyuracil is present instead of thymidine. We confirmed provirus uracil incorporation using the Uracil-qPCR assay. Stimulation of infected resting CD4 T cells showed infected cells are preventing from dividing by Vpr. Lastly, we found replication-competent virus was only produced from the initially infected parent cells instead of the divided daughter cells.

**Conclusion:** We conclude HIV can directly infect primary resting CD4 T cells. HIV-infected resting CD4 T cells incorporate uracils instead of thymidine. After T cell stimulation, Vpr prevents infected cells from dividing because it counteracts an innate lentivirus restriction mechanism against the integrated provirus through UNG2 and/or SMUG1 recognition of the incorporated uracil.

## 193 MULTIPLY INFECTED ACH2 CELLS ARE RESPONSIBLE FOR THE MAJORITY OF ACH2 HIV PRODUCTION

Joseph P. Casazza<sup>1</sup>, Avery N. Sukienik<sup>1</sup>, Quang N. Nguyen<sup>1</sup>, David R. Ambrozak<sup>1</sup>, Jianfei Hu<sup>1</sup>, Sam Darko<sup>1</sup>, Amy Ransier<sup>1</sup>, Farida Laboune<sup>1</sup>, Stephen D. Schmidt<sup>1</sup>, Daniel C. Douek<sup>1</sup>, Richard A. Koup<sup>1</sup>

<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

**Background:** ACH2 cells, A3.01 cells, singly infected by replication competent LAV, have been used as a model of latent infection. They continue to be studied because of their availability, ease of use and known proviral sequence and integration site.

**Methods:** TNF stimulated and unstimulated ACH2 cells were stained with fluorescently labeled anti-envelope mAb (PG9 and VRC01) and sorted into envelope bright, dim, and null populations. Intracellular HIV RNA was measured both using primers and probes specific for D1 unspliced, D1A4b/D1A5 and 2KB spliced RNA and by next generation read frequency. HIV insertion sites were determined by aligning chimeric reads to human genome sequence (HG38) and 5' and 3' HIV LTRs sequences with BLAST+. The frequency of proviral DNA copies per cell was estimated using the Gag/Albumin DNA ratio as determined by RT PCR.

**Results:** Even in low passage ACH2 cells, up to 12% of unstimulated ACH2 cells surface expressed HIV envelope. Env expressing cells expressed higher

levels of intracellular HIV RNA compared to non-Env expressing cells whether unstimulated or TNF stimulated. ACH2 that surface expressed Env and those that did not were easily separable by FACS sorting both before and after TNF stimulation. In the Env bright cells the proportion of read-through HIV RNA associated NT5C3A transcription was between 66-96% in the Env null population and 14-45% in the Env bright population prior to and through 9h of TNF stimulation. By sorting unstimulated ACH2 cells into Env bright and Env null population and then maintaining the Env null population in R10 with 1uM Raltegravir it was possible to establish stable populations of cells that were 1) Env negative (<5% P24 positive) and 2) Env positive (>90% P24 positive). Doubling time of Env negative and Env positive cells were similar. The relative proportion of proviral DNA/cell determined by ratio of gag DNA:albumin DNA was 7 fold higher in Env bright than Env negative cells. Production of p24 by Env negative and bright cells was 0.028 and 1.1fg/h/cell in unstimulated ACH2 and 1.7 and 59 fg/h/cell in TNF stimulated cells, respectively.

**Conclusion:** These data show that even low pass ACH2 contain a significant number of HIV-superinfected cells. These cells produce far more multiply spliced HIV RNA and far higher amounts of virus than cells which contain only 1 proviral copy and are responsible for the majority of HIV produced by bulk ACH2 cells.

## 194 miRNA'S PLASMA PROFILE ANTICIPATES LOSS OF VIROLOGICAL CONTROL IN ELITE CONTROLLERS

Jenifer Masip<sup>1</sup>, Elena Yeregui<sup>2</sup>, Reyes Jiemenez-Leon<sup>3</sup>, María C. Gasca-Capote<sup>3</sup>, Alberto Perez-Gomez<sup>3</sup>, Verónica Alba<sup>1</sup>, Anna Marti<sup>2</sup>, Montserrat Vargas<sup>2</sup>, Consuelo Viladés<sup>2</sup>, Sergi Veloso<sup>2</sup>, Joaquin Peraire<sup>2</sup>, Francesc Vidal<sup>2</sup>, Ezequiel Ruiz-Mateos<sup>3</sup>, Anna Rull<sup>2</sup>

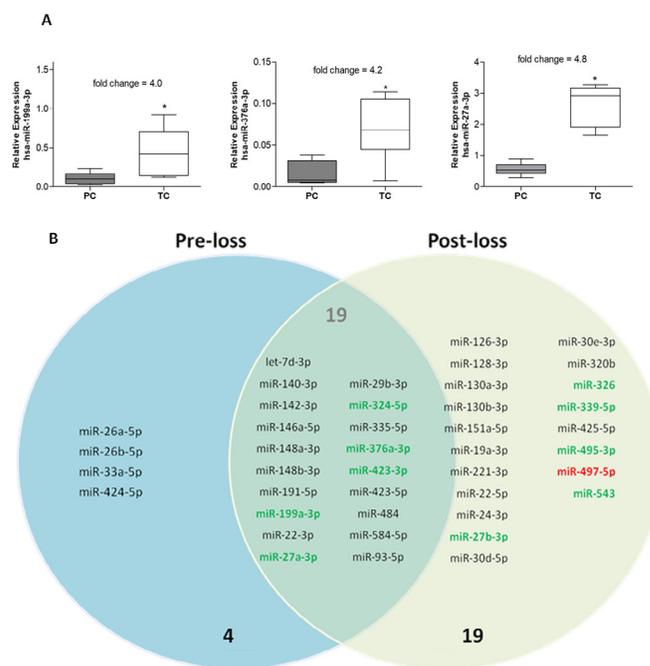
<sup>1</sup>Rovira i Virgili University, Tarragona, Spain, <sup>2</sup>Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain, <sup>3</sup>Hospital Universitario Virgen del Rocío, Sevilla, Spain

**Background:** Elite Controllers (EC) are an exceptional group of people living with HIV (PLWH) that maintain undetectable plasma HIV-1 viral loads below the detection limit while not being on antiretroviral therapy (ART). However, ECs represent a heterogeneous population in terms of virological, immunological and clinical outcomes, and around 25% of them lose virological control overtime. Thus, the aim of this study was to analyze what factors at a gene transcription level, such as miRNAs, that may lead to a loss of spontaneous viral control in PLWH-EC.

**Methods:** Plasma samples of 18 subjects from the Spanish HIV HGM BioBank belonging to the AIDS Research Network and with data in the RIS cohort of HIV Controllers Study Group (ECRIS) were included in the study. A total of 12 ECs who experienced a loss of spontaneous virological HIV-1 control (2 measurements of VL above the detection limit in 12 months) were classified as transient controllers (TC), and another group of 6 ECs who persistently maintained virological control during the same follow-up period were called persistent controllers (PC). miRNA expression profiles were obtained using TaqMan™ Advanced miRNA Human Serum/Plasma Cards.

**Results:** TC individuals showed an up-regulation of plasma miRNA profile before the loss of virological control when compared to PC. From the 23 miRNA statistically significant differentiated between groups ( $P < 0.05$ ), the most highly expressed miRNAs (fold change > 4.0) were hsa-miR-27a-3p, hsa-miR-376a-3p and hsa-miR-199a-3p, which exhibited 4.8-, 4.2- and 4.0-fold increased expression, respectively. TC after loss the spontaneous virological control also showed an up-expressed miRNA profile when compared to PC except for the hsa-miR-497-5p, which showed a downregulated expression in TC group compared to PC. Of interest, the expression of has-miR-199a-3p was highly up-regulated in TCs in both conditions, before and after (fold change = 5) the loss of virological control. Interestingly, the majority of the most highly expressed miRNAs in TC before and after the loss of virological control are related with lipid and lipoprotein metabolism.

**Conclusion:** A miRNA expression pattern associated with the spontaneous loss of virological control and also virological progression of ECs may contribute to a better understanding of clinical outcomes in PLWH-EC. A specific miRNA pattern in PLWH-EC could be used as biomarkers for a quick screening of PLWH-EC virological and immunological progression.



**Figure 1. A)** Plasma miRNA profile in PLWH-EC. Hsa-miR-199a-3p, hsa-miR-376a-3p and hsa-miR-27a-3p resulted the most highly expressed miRNAs in transient controllers (TC) before the loss of virological control compared to persistent controllers (PC). Statistical analysis was carried out by non-parametric Mann-Whitney T-test. Data is represented as box and whiskers (min to max values). **B)** Venn diagram showing the overlapping of the differentially expressed miRNAs in TC before and after the loss of virological control compared to PCs. In green upexpressed miRNAs; in red downregulated miRNAs.

## 195 IDENTIFICATION OF A NOVEL ANTI-HIV miRNA IN INTERLEUKIN-27-DIFFERENTIATED MACROPHAGES

Suranjana Goswami<sup>1</sup>, Xiaojun Hu<sup>1</sup>, Jun Yang<sup>1</sup>, Sylvain Laverdure<sup>1</sup>, Ju Qiu<sup>1</sup>, Qian Chen<sup>1</sup>, Brad T. Sherman<sup>1</sup>, Weizhong Chang<sup>1</sup>, Tomozumi Imamichi<sup>1</sup>

<sup>1</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA

**Background:** Interleukin-27 (IL-27) is a pleiotropic cytokine that influences the innate and adaptive immune systems. It inhibits viral infection and regulates the expression of microRNAs (miRNAs). We recently reported that macrophages differentiated from monocytes in the presence of IL-27 and human AB serum resisted HIV-1 infection and showed significantly enhanced autophagy.

**Methods:** CD14+ monocytes were isolated from peripheral blood mononuclear cells (PBMCs) of healthy donors and cultured in presence of 10% Human serum (AB serum) with or without 100 ng/mL IL-27 for 7 days to make AB- and ABI-Mac. Total RNA was extracted from the cells to assess micro RNA expression. MicroRNA profiles were analyzed using miRNA-seq. To assess anti-HIV effect, macrophages were transfected with synthesized microRNA mimics and then infected with HIVAD8 or a pseudotyped HIV (HIVLuc-V), and anti-HIV effect was monitored by a p24 antigen ELISA kit or luciferase assay. Induced interferon (IFN) in culture supernatants were quantified using subtype-specific ELISA kit for IFN $\alpha$ ,  $\beta$  and  $\lambda$  and autophagy assay was conducted using autophagy detection kit.

**Results:** The miRNA sequencing analysis revealed the expression of nearly 1000 known and 38 novel miRNAs. Real-time reverse transcription polymerase chain reaction (RT-PCR) analysis using probes specific to each novel miRNA confirmed that IL-27 differentially regulated the expression of 16 of the 38 miRNAs.

Overexpression of the synthesized miRNA mimics revealed that miRAB40 had potent HIV-inhibiting and autophagy-inducing properties. ELISA demonstrated that miRAB40 induced IFN- $\alpha$  (26.5 + 7.2 pg/mL), IFN- $\beta$  (6.7 + 2.2 pg/mL) but not IFN- $\lambda$ . B18R, an IFN-neutralization protein, partially suppressed both activities, although the same amount of B18R protein inhibited both activities induced by 100 pg/mL IFN- $\alpha$  &  $\beta$ , indicating that the two functions were induced via Type-I IFN-dependent and -independent pathways, respectively. To elucidate the factors associated with the IFN-independent mechanisms, miRAB40-target prediction analysis, real-time RT-PCR, and western blotting were conducted. However, we could not identify them.

**Conclusion:** We discovered a total of 38 novel microRNAs in AB mac and characterized that, dual-function miRNA, miRAB40, may provide novel insights

into the miRNA-mediated regulation of autophagy induction and HIV inhibition via IFN expression.

#### 196 RAB11-FIP1-DEPENDENT AND INDEPENDENT HIV-1 ENVELOPE TRAFFICKING

**Boris Anokhin**<sup>1</sup>, Grigoriy Lerner<sup>1</sup>, Lingmei Ding<sup>1</sup>, Paul Spearman<sup>1</sup>  
<sup>1</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

**Background:** The mechanism of incorporation of the envelope glycoprotein (Env) into HIV-1 particles is defined incompletely. Our lab has provided evidence supporting a model where Env, after synthesis and transport to the plasma membrane (PM) is endocytosed. This step is followed by trafficking through endosomal recycling compartment (ERC) to the sites of particle assembly. A cellular adaptor, Rab11-FIP1C (FIP1C), plays a key role in Env incorporation for the NL4-3 and JR-FL isolates of HIV. This study further evaluated FIP1C-dependent Env trafficking using NL4-3 and a panel of primary isolates of HIV-1.

**Methods:** HIV Env interactions with FIP1C were studied by immunofluorescence colocalization and proximity ligation assay (PLA). Env incorporation into virions and HIV replication kinetics were examined in T-cell lines.

**Results:** Using PLA we demonstrated in situ interaction of Env and FIP1C. We expressed a truncated FIP1C (FIP1C560-649) previously shown to inhibit membrane cargo exit from the ERC. A strong perinuclear PLA signal indicated that FIP1C560-649 entrapped Env in the ERC and prevented its trafficking back to the PM. The extreme C-terminal region of this construct FIP1C was critical for the interaction with HIV Env. We next examined whether FIP1C560-649 inhibited Env trafficking in primary HIV-1 isolates. Intriguingly, some HIV-1 strains escaped trapping by FIP1C560-649. To determine if the FIP1C-independent strains still required transit through the ERC, we utilized a catalytically inactive ubiquitin ligase RFL that has been shown to halt recycling of cargo from the ERC to the PM. Expression of RFL resulted in a collapsed, perinuclear ERC that retained Env derived from both FIP1C-dependent and FIP1C-independent isolates. We also targeted the C-terminal region of FIP1C in H9 cells using CRISPR/Cas9. Upon infection of knockout cells with NL4-3, a significant reduction in Env incorporation into virions was observed, and viral replication in culture was markedly diminished.

**Conclusion:** The present work indicates that trafficking through the ERC is a critical step for incorporation of Env into HIV-1 particles. PLA results suggest a direct interaction between Env and FIP1C. While all HIV-1 Env isolates require recycling from the ERC, some utilize FIP1C as an essential recycling adaptor, but others do not. We speculate that alternative recycling adaptors are involved in the incorporation of Env into particles for FIP1C-independent HIV-1 isolates.

#### 197 IRON CHELATOR PPyET INHIBITS HIV-1 REPLICATION IN HUMANIZED MICE

**Namita Kumari**<sup>1</sup>, Miguel D. Rougvié<sup>2</sup>, Songping Wang<sup>1</sup>, Douglas Nixon<sup>2</sup>, Fatah Kashanchi<sup>3</sup>, Sergei Nekhai<sup>1</sup>  
<sup>1</sup>Howard University, Washington, DC, USA, <sup>2</sup>Weill Cornell Medicine, New York, NY, USA, <sup>3</sup>George Mason University, Fairfax, VA, USA

**Background:** Targeting host cell factors involved in HIV-1 replication holds promise for HIV-1 inhibition, as no resistance is expected. An emerging factor of interest is p21, which controls cell cycle progression and which levels were increased in HIV-1 elite controllers. A 25-hydroxycholesterol (25HC) is a soluble antiviral factor, which is formed by CH25H from cholesterol and blocks HIV-1 fusion. Administration of 25HC to humanized mice suppresses HIV-1 replication and reverses T cell depletion. We previously showed that Phenyl-1-Pyridin-2yl-Ethanone-Based iron chelators, PPyET and PPyAT, inhibit HIV-1 replication by inducing expression of Ikbα and p21.

**Methods:** We used a custom designed array of 42 known restriction factors to analyze the effect of PPyET on regulation of these restriction factors of HIV-1. Further we knocked down the identified factors (p21 or CH25H) and then carried out HIV-1 infection in presence of PPyET to confirm the role of these factors in PPyET mediated HIV-1 inhibition. Finally, humanized mice were infected with HIV-1 and PPyET was administered intraperitoneally to confirm in-vivo role of PPyET in HIV-1 restriction.

**Results:** Significant upregulation of p21 and CH25H was observed in PPyET treated THP-1 cells. Knockdown of p21 or CH25H reversed HIV-1 inhibition by PPyET, further suggesting that these factors mediated HIV-1 inhibition by PPyET. Treatment with non-related protein phosphatase-1 targeting compound 1E7-03 inhibited HIV-1 in p21 or CH25H knockdown cells. PPyET treatment significantly suppressed HIV-1 replication in PBMC and THP-1 derived macrophages infected

with HIV-1(HIB) and HIV-1(B-al). In vivo, intraperitoneal administration of PPyET reduced HIV-1 replication as reflected by reduced levels of HIV-1 TAR RNA, env mRNA and gag mRNA in humanized PBMC-reconstituted NSG mice.

**Conclusion:** Iron chelator PPyET inhibits HIV-1 replication by inducing levels of p21 and CH25H. It showed efficacy in HIV-1 infected humanized mice, suggesting its utility in future antiretroviral therapy.

#### 198 QUANTITATIVE PHOSPHOPROTEOME ANALYSES OF PP1-TARGETING HIV-1 INHIBITOR 1E7-03

**Xionghao Lin**<sup>1</sup>, Tatiana Ammosova<sup>1</sup>, Songping Wang<sup>1</sup>, Andrey I. Ivanov<sup>1</sup>, Sergei Nekhai<sup>1</sup>  
<sup>1</sup>Howard University, Washington, DC, USA

**Background:** Human immunodeficiency virus-1 (HIV-1) establishes long-lived stable reservoirs that can be reactivated when combination antiretroviral therapy (cART) is interrupted or drug resistance appears. Transcription activation is an essential step in the reactivation of latent HIV-1, and transcription inhibition might facilitate HIV-1 cure or prevent HIV-1 related pathogenesis. We identified a novel small molecule, 1E7-03, that binds to the RVxF site of protein phosphatase 1 (PP1) and inhibits HIV-1 transcription in CEM T cells (IC<sub>50</sub> = 4.5 μM). 1E7-03 also reduces HIV-1 replication in HIV-1 infected humanized mice by about 40-fold. 1E7-03 prevents PP1 from shuttling into nucleus facilitated by HIV-1 Tat protein. However, the overall host cellular response to 1E7-03 has not been investigated.

**Methods:** We performed label-free quantitative phosphoproteomics and proteomics analysis of non-infected cells and HIV-1 infected cells that were untreated or treated with 1E7-03. The phosphorylation quantitative analysis was carried with no enrichment (NER), or with phosphopeptides enriched on Fe-NTA or TiO<sub>2</sub>. The phosphorylation of the selected candidate proteins was further validated using Western blot (WB) with okadaic acid (OA) as a positive control.

**Results:** 1E7-03 significantly reprogrammed the cellular phosphoproteome but did not change host proteins expression levels. Biological pathway analysis showed that phosphorylation of proteins within TGF-β and PPARα/RXRα signaling pathways was primarily affected by 1E7-03. In TGF-β signaling pathway, 1E7-03 significantly decreased phosphorylation levels of TGF-β2 on Ser-46 (~12.02-fold, p=1.37E-03). In PPARα/RXRα pathway, phosphorylation of Nucleophosmin 1 (NPM1) at Ser-125 was significantly downregulated (~20.15-fold, p=1.37E-09). The downregulation of NPM1 phosphorylation in the cells treated with 1E7-03 was further confirmed by WB analysis.

**Conclusion:** We have identified TGF-β and PPARα/RXRα signaling pathway as being primarily affected by PP1-targeting HIV-1 transcription inhibitor 1E7-03 using global quantitative phosphoproteomics and proteomics. TGF-β2 and NPM1 have been associated with HIV-1 transcription activation, and reported as PP1 partners or substrates. Therefore, targeting phosphorylation of host proteins such as TGF-β2 and NPM1 might serve as a novel approach to achieve HIV-1 transcription inhibition.

#### 199 A SORTING SIGNAL IN THE SIV Env TAIL IS SELECTED IN VIVO DURING PATHOGENIC INFECTION

**Scott P. Lawrence**<sup>1</sup>, Samra Elser<sup>2</sup>, Pyone Aye<sup>3</sup>, Faith Schiro<sup>4</sup>, Brandon Keele<sup>5</sup>, James Hoxie<sup>2</sup>, Mark Marsh<sup>1</sup>, Nicholas Maness<sup>3</sup>  
<sup>1</sup>University College London, London, UK, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>Tulane University, Metairie, LA, USA, <sup>4</sup>Tulane National Primate Research Center, Covington, LA, USA, <sup>5</sup>National Cancer Institute, Frederick, MD, USA

**Background:** The cytoplasmic tail of HIV and SIV Envs contain a highly conserved Tyr-dependent sorting motif, YxxØ (x= any a.a.; Ø= an a.a. with a bulky hydrophobic side chain) that mediates clathrin-dependent endocytosis and basolateral sorting of Env. Deletion of Gly and Tyr from this motif in SIVmac239 Env (a.a.720-721), creating a virus termed ΔGY, resulted in a novel phenotype in pigtail macaques (PTM) characterized by preservation of gut and blood CD4+ T cells followed by host control and an absence of disease despite robust acute viral replication. Rarely, ΔGY-infected PTM progressed to AIDS in association with an R722G Env mutation and deletion of three codons (corresponding to a.a.734-736; QTH) that overlap the rev and tat orfs and create novel YFQI or YFQL sequences reminiscent of the parental YxxØ (Fig.1). We hypothesized ΔGY Env had impaired trafficking properties that were reconstituted by the in vivo mutations. We assessed the consequences of these changes in vitro and in vivo.

**Methods:** Env expression was assessed using infected cell lines. Reporter constructs previously validated for quantifying trafficking of SIV/HIV Envs, were used to assess the impact of R722G and ΔQTH Env mutations. PTM were inoculated with ΔGY containing R722G ± ΔQTH and animals followed for plasma viral RNA and viral evolution.

**Results:** In vitro, the ΔGY mutation decreased Env content in cells and on virions by 40%. An R722G mutation restored Env expression but had no effect on Env trafficking. In contrast, the ΔQTH mutation reconstituted potent Tyr-dependent signals for both endocytosis and basolateral sorting. In PTM, ΔGY containing both R722G and ΔQTH Env mutations was associated with high viral loads and were maintained throughout infection. Two animals that received ΔGY containing only R722G developed high viral loads and AIDS in association with further mutations: One animal developed a ΔQTH; the second acquired three point mutations creating a novel motif (IRL; Fig.1) that conferred basolateral sorting but not endocytosis. In vivo, when introduced onto a ΔGY background the IRL mutations were completely conserved and sufficient to maintain high viral loads in four PTM.

**Conclusion:** These findings reveal strong selection pressures on signals for Env endocytosis and basolateral sorting and reveal a previously unappreciated role for polarized cellular trafficking of Env during pathogenic lentivirus infection.

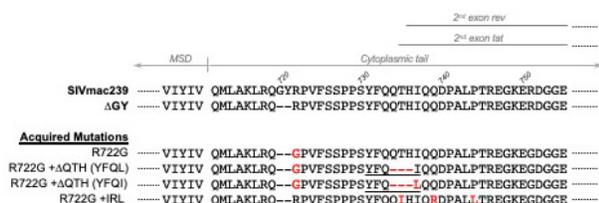


Fig 1. Mutations acquired in Env cytoplasmic tail in ΔGY-infected Macaques that progressed to disease (MSD – Membrane spanning domain).

## 200 ADOPTIVE TRANSFER OF GAMMA DELTA T CELLS ENHANCES HIV INFECTION IN A HUMANIZED MOUSE

Shivkumar Biradar<sup>1</sup>, Yash Agarwal<sup>1</sup>, Moses T. Bility<sup>1</sup>, Robbie B. Mailliard<sup>1</sup>  
<sup>1</sup>University of Pittsburgh, Pittsburgh, PA, USA

**Background:** Human gamma-delta (γδ) T cells can mediate potent antiviral effects in an MHC-independent manner, making them attractive for immunotherapeutic application to treat chronic HIV infection. In vitro studies demonstrated the cytotoxic capacity of Vδ2 T cells against HIV infected targets. However, in vivo translational studies defining the antiviral properties of these cells are lacking. Here, we optimized a humanized mouse model to study the immunologic role, functional status, and immunotherapeutic potential of γδ T cells in the setting of HIV infection.

**Methods:** Bone-marrow, Liver, Thymus (BLT) humanized mice (huMice) were generated by engrafting NSG mice with autologous hHSCs via retro-orbital injection, and with human lymphoid tissues (fetal thymus and liver) for hematopoiesis via kidney capsule transplant. Reconstitution, phenotype, and function of human immune cells were characterized by flow cytometry analysis. The immunotherapeutic potential of γδ T cells was assessed by adoptive transfer of HIV-infected CD4 T cells and ex-vivo expanded allogeneic Vδ2 T cells into huMice. Blood samples from HIV-infected huMice were analyzed by flow cytometry and qRT-PCR to measure changes in the frequency and phenotype of human T cells and HIV viral load, respectively.

**Results:** We provide the first characterization of successfully reconstituted γδ T cell subsets in the peripheral blood and lymphoid tissue of BLT huMice, and we demonstrate an HIV-associated depletion of Vδ2 T cells and increase in Vδ1 cells in the blood following infection. The functionality of human Vδ2 T cells isolated from the murine spleen of huMice was confirmed via ex vivo activation and proliferation with exposure to allogeneic monocytes, zoledronate, and IL-2. Unexpectedly, the adoptive transfer of expanded allogeneic Vδ2 T cells from uninfected human donors resulted in an increase in HIV viremia in HIV-infected BLT huMice. We determined that the in vivo exposure of the huMice to HIV resulted in the upregulation of CD4 expression on the human Vδ2 T cells and their direct susceptibility to HIV infection.

**Conclusion:** The robust reconstitution of γδ T cells can be achieved in BLT huMice for studying HIV and γδ T cell interactions. Our data suggest that activated Vδ2 cells can serve as an early target for HIV infection to play a critical role in the early stages of viral dissemination and HIV reservoir establishment.

This model provides a platform for in vivo evaluation of γδ T cell-based therapies targeting human diseases.

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

Alexandra Ortiz<sup>1</sup>, Phillip Baker<sup>1</sup>, Charlotte Langner<sup>1</sup>, Jennifer Simpson<sup>1</sup>, Jacob Flynn<sup>1</sup>, Carly E. Starke<sup>1</sup>, Carol Vinton<sup>1</sup>, Brandon Keele<sup>2</sup>, Jason Brenchley<sup>1</sup>

<sup>1</sup>National Institutes of Health, Bethesda, MD, USA, <sup>2</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA

**Background:** Alteration 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.

**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.

**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 and IgA+ B-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.

**Conclusion:** These findings experimentally demonstrate that intestinal dysbiosis contributes to alteration to gastrointestinal tract immunity and lentiviral acquisition across the epithelial barrier.

## 202 FULLY QUANTITATIVE PET IMAGING UNRAVELS THE RELATIVE SIZE OF GUT CD4 POOL

Sharat Srinivasula<sup>1</sup>, Insook Kim<sup>1</sup>, Paula Degrange<sup>2</sup>, Bradley Long<sup>2</sup>, Jorge A. Carrasquillo<sup>3</sup>, Cliff Lane<sup>4</sup>, Michele Di Mascio<sup>2</sup>

<sup>1</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, <sup>3</sup>National Cancer Institute, Bethesda, MD, USA, <sup>4</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

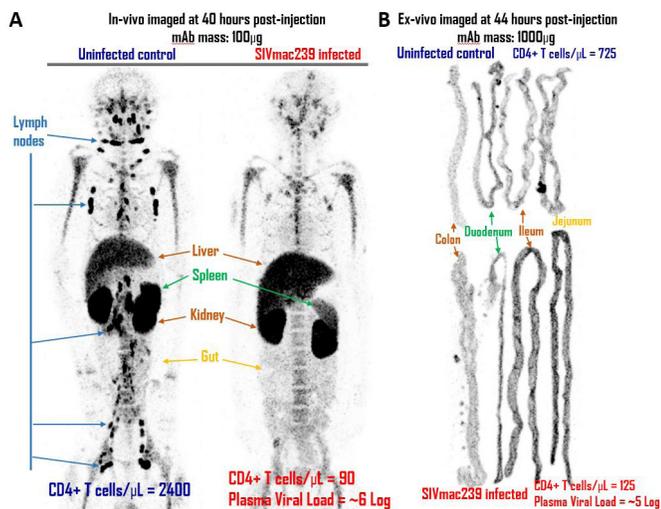
**Background:** Previous studies have yielded conflicting results regarding the contribution of the gut to the overall CD4+ T-cell pool. SPECT imaging of whole-body CD4-pool in monkeys (by our group) using an anti-CD4 antibody (mAb) fragment (CD4R1-F(ab)'<sub>2</sub>) radiolabeled with Technetium-99m revealed low CD4-pool in the small and large intestines, corroborated by ex-vivo data. In contrast, PET imaging (by others) using the same anti-CD4R1 fragment radiolabeled with Copper-64 revealed substantial uptake in the gut of healthy animals and reduced uptake following SIV infection. The probe uptake in the clusters of lymph nodes and the spleen were similar between the two studies. Using a novel PET camera designed for monkeys (Mediso) with higher spatial resolution compared to clinical SPECT and PET cameras, we have repeated our experiments with the same anti-CD4R1 fragment radiolabeled with Zirconium-89 (89Zr).

**Methods:** The CD4R1-F(ab)'<sub>2</sub> was radiolabeled with 89Zr using desferrioxamine with an isothiocyanate linker. Probe affinity was tested in MT4 cells. Healthy (n=6) or SIV-infected (n=3) rhesus macaques (CD4+T cells/μl: 90-2400) received intravenous injections of 58-127 MBq of 89Zr-CD4R1-F(ab)'<sub>2</sub> (mAb-dose: ~100microg for five animals and ~1000 microg for the remaining four) and in-vivo imaged up to 6 days post-injection. PET-dynamic imaging coupled with kinetic modeling was performed to estimate binding potential (BP), the product of CD4 receptor molarity and ligand affinity.

**Results:** 3D PET images of the CD4-pool revealed a clear delineation of lymph nodes and spleen, with dramatic differences of probe uptake in these organs between the healthy and the infected animals (Figure). Consistent with previous images obtained with 99mTc-CD4R1-F(ab)'<sub>2</sub>, regardless of the mAb dose, the new 89Zr-CD4R1-F(ab)'<sub>2</sub> uptake in the gut was low and did not differ between healthy and SIV-infected animals. Ex-vivo studies of large and small intestines confirmed the in-vivo images. BP estimates showed the gut's

contribution to the total CD4 pool in humans to be lower than the spleen's contribution alone.

**Conclusion:** The vast majority of specific binding to CD4+ tissue was localized to lymph nodes and spleen with minimal uptake in the gut. Gut uptake did not change in the setting of SIV infection. These data suggest that the prevalent notion of the gut as a major reservoir of the CD4 pool in the body needs to be revised.



**203 PRE-ART VIRAL LOAD IS PREDICTIVE OF LYMPH NODE ART LEVELS IN SIV-INFECTED MACAQUES**

**Sharat Srinivasula**<sup>1</sup>, Paula Degrange<sup>2</sup>, Andrew Bonvillian<sup>2</sup>, Amanda Tobery<sup>2</sup>, Jacob Kaplan<sup>2</sup>, Claire Deleage<sup>1</sup>, Angela D. Kashuba<sup>3</sup>, Mackenzie L. Cottrell<sup>1</sup>, Michele Di Mascio<sup>2</sup>

<sup>1</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, <sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** Using dual-photon in-vivo imaging, we previously showed significantly lower concentrations of tenofovir (TFV) in rat lymph nodes (LN) compared to peripheral blood (PB). This finding was later confirmed for intracellular active drug-metabolite (IADM) levels of nucleos(t)ide reverse transcriptase inhibitors (NRTIs) in antiretroviral (ARV) therapy (ART) of HIV/SIV. Understanding factors that regulate penetration of NRTIs across the blood-lymphatic barrier can assist the development of new formulations (e.g. lipid-based nanoparticles) optimized for HIV treatment and prevention. **Methods:** We retrospectively analyzed ARV levels in 21 Indian rhesus macaques (RMs) infected with SIVmac239nefstop and treated with daily ART (20mg/kg,SQ,TFV, 30mg/kg,SQ,emtricitabine (FTC), and 100mg,P.O.,integrase inhibitor L-870812) starting at week 5 post-infection (M0) for 3 months (Di Mascio et al., Science 2019). We quantified TFV and FTC in plasma and their IADMs (TFV-diphosphate, TFV-dp; FTC-triphosphate, FTC-tp) in PBMC and LN mononuclear cells (LNMC) by HPLC-MS/MS at month 1 (M1) and month 3 (M3) post-ART initiation. Collagen type-1 in LN at M0 was measured. Viral load in plasma, LN and rectal tissue (SIV-RNA copies/10<sup>6</sup> cell eq.), and %Ki67+ in PB CD4T, CD8T, and CD20B cells were measured.

**Results:** TFVdp and FTCtp concentrations were significantly lower in the LNMC compared to PBMC (median;M1: 3 and 12-fold, M3: 2 and 7-fold, respectively;p≤0.005). Between M1 and M3, viral RNA decreased in LN, and IADM levels increased in both LNMC (2-3-fold, p≤0.001) and PBMC (1.4-1.5-fold, p≤0.01). LNMC IADM levels at M1 were inversely correlated with plasma viremia (TFVdp: p=0.003, FTCtp: p=0.07), LN (TFVdp: p=0.06, FTCtp: p<0.05) and rectal tissue (p<0.05) viral load at ART initiation, but not collagen deposition or PB %Ki67+. Yet, LNMC IADM levels at M1 were not predictive of viral decay rates during ART. A larger reduction in PB %Ki67+ in CD4T cells during M1 was associated with higher LNMC IADM levels at M1 (p<0.05).

**Conclusion:** NRTI IADM levels were consistently lower in LNMC vs. PBMC of SIV-infected and ART-treated RMs. Viral clearance during the first 3 months of ART corresponded with increasing IADM levels in LNMC and to a lesser extent in PBMC. Given the human and macaque models showing the IADM loading

phase of ~1 week in PBMC and rectal tissue, these data suggest a link between viral dissemination/viral-induced generalized immune activation and drug penetration in LNs, a major reservoir of viral replication.

**204 ALTERED RESPONSE PATTERN FOLLOWING NONCANONICAL NF-κB ACTIVATION IN INFANT MACAQUES**

**Katherine M. Bricker**<sup>1</sup>, Brianna Williams<sup>1</sup>, Danielle Oliver<sup>1</sup>, Veronica Obregon-Perko<sup>1</sup>, Brian Van Horne<sup>2</sup>, Amanda P. Shauer<sup>2</sup>, Lauren Tompkins<sup>2</sup>, Mackenzie L. Cottrell<sup>2</sup>, David M. Margolis<sup>2</sup>, Richard M. Dunham<sup>3</sup>, Ann Chahroudi<sup>1</sup>

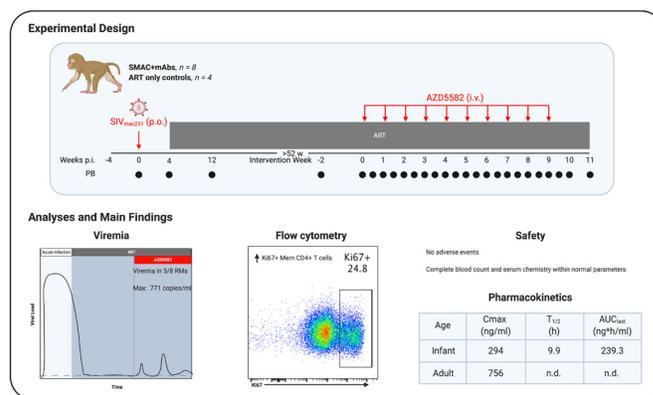
<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>ViiV Healthcare, Research Triangle Park, NC, USA

**Background:** Strategies to eradicate or control the persistent HIV reservoir, the major obstacle to cure, would be highly beneficial for the 1.8 million children living with HIV. The "shock and kill" approach combines a latency reversing agent (LRA) to reactivate CD4+ T cells harboring integrated HIV-1 DNA with a clearance agent to enhance the immune-mediated elimination of infected, reactivated cells. Recent work in our lab identified a mimetic of the second mitochondrial-derived activator of caspases (SMACm), AZD5582, as an effective LRA in adult rhesus macaques. LRAs have not yet been evaluated in pediatric clinical or preclinical studies.

**Methods:** We evaluated the SMACm AZD5582 in 8 SIV-infected, ART-suppressed infant rhesus macaques (RM) compared to 4 ART-only controls. Infants were orally challenged with SIVmac251 at 4 weeks of age and treated with a suppressive triple ART regimen for over 1 year beginning 4 weeks post infection. SMACm treated animals received 10 weekly doses of AZD5582 i.v. at 100 µg/kg. Viral loads, Ki67 expression on CD4+ T cells, and AZD5582 concentrations were measured longitudinally to assess AZD5592 response.

**Results:** SMACm treated infants had similar viral loads at ART initiation as adult RMs that showed on-ART viremia following AZD5582 treatment (p = 0.72). Treatment with AZD5582 during ART was safe in our pediatric model, with no adverse clinical events. A significant increase in Ki67 expression on memory CD4+ T cells was observed 3d post-dose 1, 3, and 6 (p = 0.04). The first incidence of viremia >60 copies/ml was observed 3d following dose 4 with transient viremia observed in 5/8 treated RMs (63%, max = 771 copies/ml). Out of 135 viral load measurements performed on the 5 RMs that exhibited on-ART viremia during AZD5582 treatment, 8 were >60 copies/ml (6%), lower than the 46% we have observed in adult RMs. Plasma concentrations of AZD5582 indicate altered pharmacokinetics in infants compared to adults (C<sub>max</sub> = 294 ng/ml vs 756 ng/ml, respectively).

**Conclusion:** In summary, we have demonstrated that despite similar predicted reservoir size and expected pharmacodynamics, alterations in the pharmacokinetic profile of AZD5582 may lead to dampened latency reversal in infant RMs. These results support a growing body of evidence that distinctions in the pediatric viral reservoir may result in divergent or blunted responses to LRAs in HIV-1-infected children and highlight the importance of pediatric models to evaluate HIV-1 cure interventions.



## 205 TIMELY ACQUISITION OF MYELOID-CELL IMMUNE-REGULATORY PHENOTYPE AND COVID-19 OUTCOME

Amelia Chiara Trombetta<sup>1</sup>, Guilherme B. Farias<sup>1</sup>, André MC Gomes<sup>1</sup>, Ana Godinho-Santos<sup>1</sup>, Pedro Mota Prego Rosmaninho<sup>1</sup>, Carolina M. Conceição<sup>1</sup>, Júlio Joel Laia Henriques<sup>1</sup>, Diana F. Santos<sup>1</sup>, Maria Ines Tostão Neiva<sup>1</sup>, Afonso RM Almeida<sup>1</sup>, Ana E. Sousa<sup>1</sup>, Susana Mendes Fernandes<sup>1</sup>

<sup>1</sup>Instituto de Medicina Molecular, Lisbon, Portugal

**Background:** Uncontrolled inflammatory responses, ranging from cytokine storm to immune-paralysis were described in COVID-19 worse prognosis. Patients with an aggressive course are the bottleneck of COVID-19 pandemic management, and there is urgent need of understanding the underlying mechanisms to guide clinical decisions. Myeloid cell activation is likely a key player in SARS-CoV-2 infection.

**Methods:** Here, we longitudinally evaluated COVID-19 patients with respiratory insufficiency admitted to Hospital Santa Maria (Lisbon, Portugal), comparing those that did not require intensive care admission (NO-ICU) with those requiring high flux oxygen and/or mechanical ventilation (ICU). At each time point, an ex-vivo immune-phenotype by flow cytometry was analysed with both supervised and unsupervised approaches and clustering analysis of circulating cell subsets of monocytes (Mo) and dendritic cells (DCs), in parallel with specific antibody responses and a wide array of inflammatory mediators.

**Results:** Contrarily to other systemic viral infections, we found that COVID-19 patients with respiratory insufficiency featured systemic immune-suppressive/regulatory myeloid cell responses. Specifically, we observed a global reduction of CD14lowCD16+ Mo, and reduced expression of CD80, CD86, and SLAN.

Contemporaneously, both Mo and DC showed increased expression of CD163, CD204, CD206 and PD-L1 immune-regulatory markers. Moreover, cDC2s, pDCs and basophils were significantly reduced. Inflammatory cytokines and chemokines associated with myeloid cell chemotaxis correlated with the phenotype changes. In NO-ICU patients (n=9) we observed a peak of these alterations at admission and a progressive regression to healthy phenotype at hospital discharge (as compared to age-matched controls, n=11). On the other hand, in ICU patients (n=11), the expression of immuno-suppressive markers progressively increased until discharge. Notably, they featured significant reduction of HLA-DRhighPD-L1- and expansion of CD80-CD86- classical Mo and an increase of HLA-DRhighPD-L1+ cells in Mo and in all DC subsets at recovery.

**Conclusion:** Altogether, these data favour an alternative view of a beneficial role of suppressive/regulatory myeloid responses in coping with COVID-19 pathogenesis. To further support our hypothesis, we are currently collecting data on lung injury and SARS-CoV-2 viremia to correlate with the kinetics of myeloid responses.

## 206 SUPPRESSION OF ACE2 FUNCTION AND ANTIVIRAL IMMUNE RESPONSE BY SARS-CoV-2 INFECTION

Lucía Gutiérrez Chamorro<sup>1</sup>, Eva Riveira-Muñoz<sup>1</sup>, Vansea Palau<sup>2</sup>, Marta Massanella<sup>1</sup>, Edurne Garcia-Vidal<sup>1</sup>, Roger Badia<sup>1</sup>, Sònia Pedreño-López<sup>1</sup>, Jordi Senserrich<sup>1</sup>, Bonaventura Clotet<sup>1</sup>, Cecilia Cabrera<sup>1</sup>, Marta Crespo<sup>2</sup>, Julio Pascual<sup>2</sup>, Marta Riera<sup>2</sup>, Ester Ballana<sup>1</sup>

<sup>1</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>2</sup>Hospital del Mar, Barcelona, Spain

**Background:** SARS-CoV-2 receptor angiotensin-converting-enzyme 2 (ACE2) is also a protective factor that contributes to reduce inflammation and fibrosis in tissues. An active form of ACE2 can be released from the cell surface by host proteases ADAM17 and TMPRSS2, being the latter also necessary for viral entry. Due to its properties, the administration of soluble recombinant ACE2 has been proposed as a SARS-CoV-2 treatment. Here, we assess the role of ACE2 activity and antiviral immune response at the site of infection in nasopharyngeal swabs of SARS-CoV-2 patients, to unravel its effect on inflammation cascade and infection outcome.

**Methods:** Soluble enzymatic activity of ACE2 was measured in nasopharyngeal swabs at the time of PCR positivity (mean time from symptom=4d) and 3 days after in a cohort of mild SARS-CoV-2 patients (n=40, mean age=42y) and in uninfected controls. Gene expression profiles of ACE2, its proteases, ADAM17 and TMPRSS2, and interferon-stimulated genes (ISGs), DDX58, CXCL10 and IL-6 were also evaluated by RT-qPCR.

**Results:** Both ACE2 activity and mRNA expression decreased significantly during infection course in paired samples of SARS-CoV-2 infected subjects (p=0.048 and p<0.001, respectively), although differences between infected and uninfected subjects were only seen at mRNA level (p<0.001). Importantly,

both ACE2 activity and mRNA expression showed a positive correlation with viral load (rho=0.352, p-value=0.0259), suggesting that viral infection is influencing ACE2 function. Similarly, infection downregulates TMPRSS2 expression (p-value<0.01), but not ADAM17, further indicating the viral-induced regulation of host receptors. In contrast to ACE2 data, a clear induction of IFN stimulated genes, CXCL10, IL-6 and DDX58 (RIG-I), is observed upon infection (p-value<0.05 in all cases), demonstrating that SARS-CoV-2 induces an antiviral response and suggesting that ACE2 is not an ISG. This increased expression of ISGs is directly linked to viral load (rho=0.6177, p-value<0.0001; rho=0.4026, p-value=0.0110; rho=0.3024, p-value=0.0613, respectively) but it is rapidly reversed during infection course.

**Conclusion:** Overall, our results demonstrate the existence of mechanisms by which SARS-CoV-2 suppress ACE2 expression and function, intracellular viral detection and subsequent ISG induction, offering new insights into ACE2 dynamics and inflammatory response in the human upper respiratory tract that may contribute to understand the early antiviral host response to SARS-CoV-2 infection.

## 207 FUNCTION, HOMING, AND RESIDENCY OF T-CELL IMMUNE RESPONSES AGAINST SARS-CoV-2

Nerea Sánchez-Gaona<sup>1</sup>, Judith Grau-Expósito<sup>1</sup>, Nuria Massana<sup>1</sup>, Marina Suppi<sup>1</sup>, Antonio Astorga Gamaza<sup>1</sup>, David Perea<sup>1</sup>, Joel Rosado<sup>2</sup>, Anna Falcó<sup>2</sup>, Cristina Kirkegaard<sup>2</sup>, Jordi Navarro<sup>2</sup>, Vicenç Falcó<sup>2</sup>, Joaquin Burgos-Cibrian<sup>2</sup>, Maria José Buzón<sup>1</sup>, Meritxell Genescà<sup>1</sup>

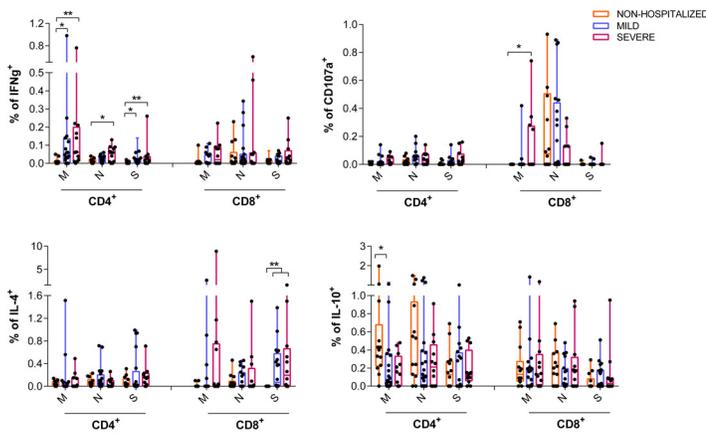
<sup>1</sup>Vall d'Hebron Research Institute, Barcelona, Spain, <sup>2</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain

**Background:** In order to inform vaccine development on the correlates of protection against SARS-CoV-2, we performed detailed phenotypic and functional analyses in clinically-defined groups of patients recruited during the first wave of SARS-CoV-2 infection, including the assessment of Resident Memory T cells (TRM) in lung of convalescent patients.

**Methods:** Blood samples from 46 participants diagnosed with acute COVID-19 (14 symptomatic non-hospitalized; 20 mild-hospitalized and 12 severe-hospitalized) were obtained 7-16 days after symptoms onset. Lung biopsies were obtained from three convalescent patients 1 to 7.5 months after initial infection. The phenotype and functional capabilities of SARS-CoV-2-specific CD4+ and CD8+ T cells were measured by FACS after stimulation with a pool of overlapping SARS-CoV-2 viral peptides (M, N and S).

**Results:** Pattern variations associated with viral-specific T cell responses were based on two factors, the targeted viral protein and the cohort of patients assessed. Overall, stimulation with M and N viral peptides induced a Th1 profile exemplified by IFN $\gamma$  production in CD4+ T cells and degranulation in CD8+ T cells respectively, whereas S peptides induced a Th2 profile exemplified by IL-4. Hospitalized patients showed increased IFN $\gamma$  secretion in CD4+ T cells in response to any viral protein compared to non-hospitalized patients (p=0.020 for M and S peptides in the mild group; p=0.004 for M, p=0.011 for N and p=0.007 for S peptides in the severe group; Figure 1) and IL-4 secretion in CD8+ T cells in response to S peptides (p=0.004 and p=0.003 for mild and severe patients, respectively). In contrast, the expression of IL-10, which was mostly expressed in CCR7+ cells, was significantly increased in CD4+ T cells from non-hospitalized patients after stimulation with M peptides when compared to the mild COVID-19 group (p=0.035). Importantly, SARS-CoV-2 specific T cell responses with a biased TRM profile were detected up to 7.5 months after infection in the lung of convalescent patients. However, tissue responses strongly differed from blood.

**Conclusion:** Our results suggest that a balanced anti-inflammatory antiviral response promoted by non-spike proteins may be key to favor infection resolution without major complications. Further, while immune responses migrate and establish in the lung as resident memory T cells, the magnitude and profile of the lung SARS-CoV-2 specific T cells strongly differ from the response detected in blood.



**208 COMPARTMENTAL T-CELL PROFILE AND IFN RESPONSE IN SARS-CoV-2- INFECTED SUBJECTS**

**Letizia Santinelli**<sup>1</sup>, Francesca Sciarra<sup>1</sup>, Claudia Pinacchio<sup>1</sup>, Giuseppe P. Innocenti<sup>1</sup>, Giuseppe Oliveto<sup>1</sup>, Mirko Scordio<sup>1</sup>, Federica Frasca<sup>1</sup>, Guido Antonelli<sup>1</sup>, Claudio M. Mastroianni<sup>1</sup>, Alessandra Pierangeli<sup>1</sup>, Carolina Scagnolari<sup>1</sup>, Andrea Isidori<sup>1</sup>, Mary A. Venneri<sup>1</sup>, Gabriella D’Ettore<sup>1</sup>, Giancarlo Ceccarelli<sup>1</sup>  
<sup>1</sup>Sapienza University of Rome, Rome, Italy

**Background:** A severe SARS-CoV-2 related immunopathology may be the driver cause underlying the deleterious clinical manifestations observed in COVID-19 patients. To identify possible tissue-specific immune responses patterns, a compartmental immunophenotyping analysis of CD4+ and CD8+ T lymphocytes and IFN response has been performed in SARS-CoV-2 infected subjects with acute respiratory distress syndrome.

**Methods:** Bronchoalveolar lavage (BAL) and Peripheral Blood Mononuclear Cells (PBMC) samples were collected from 13 SARS-CoV-2 infected subjects (9 males and 4 females) consecutively admitted to intensive care unit (ICU) of Policlinico Umberto I, Sapienza University Hospital in Rome (Italy). The frequencies of CD4+, CD8+ T lymphocytes and those expressing immune activation markers (CD38, HLADR), naïve, central memory (CMEM), and effector memory (TEM) T cell subsets were evaluated in both anatomical sites by multi-parametric flow cytometry. Gene expression levels of Interferon regulatory factor 7 (IRF7) and the Interferon Stimulated Gene 15 (ISG15) were evaluated in BAL and PBMC by Real-time PCR.

**Results:** Critically SARS-CoV-2 infected patients exhibited a lung compartmentalization of CD8+ T cells (p=0.003), with a lower CD4/CD8 ratio in BAL compared to blood district (p<0.01). However, higher frequencies of CD8+ T cells were recorded in PBMC of female SARS-CoV-2 infected patients (p=0.04) and the same trend was observed in the lung compartment. By contrast, a trend of increasing CD4+ T cells frequencies was observed in BAL samples of male patients, as opposed to blood compartment. Additionally, an increased expression of immune activation markers CD38 and HLADR has been detected in BAL CD8+ T cells (p<0.01) as well as in blood CD4+ T cells (p=0.03). An increased frequency of CD4+ and CD8+ TEM cells has been documented in BAL of SARS-CoV-2 infected patients (p<0.05), as opposed to higher frequencies of CD4+ and CD8+ TCM cells recorded in the blood compartment (p<0.01). Notably, higher levels of ISG15 and IRF7 found in BAL were inversely associated to activated CD8+ T cell frequencies in the lung compartment compared to blood district (ISG15: r=-0.570, p<0.05) (IRF7: r=-0.683, p=0.01).

**Conclusion:** Our findings provide new insight into a distinct T cells profile and IFN genes expression in the lung and in the blood compartment of SARS-CoV-2 infected patients, that might be highly relevant for the clinical course of COVID-19.

**209 HOST FACTORS ASSOCIATED WITH PERSISTENT SARS-CoV-2 VIRAL RNA IN COVID-19 OUTPATIENTS**

**Annukka A. Antar**<sup>1</sup>, Tong Yu<sup>1</sup>, Razvan Azamfirei<sup>1</sup>, Nora Pisanic<sup>2</sup>, Jeffrey A. Tornheim<sup>1</sup>, Kirsten Littlefield<sup>2</sup>, Sabra L. Klein<sup>2</sup>, Andrew Pekosz<sup>2</sup>, Christopher D. Heaney<sup>2</sup>, Chen Hu<sup>1</sup>, Mei Cheng Wang<sup>2</sup>, Paul Blair<sup>1</sup>, David L. Thomas<sup>1</sup>, Yukari C. Manabe<sup>1</sup>, for the Ambulatory COVID Study Team

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Sustained molecular detection of SARS-CoV-2 RNA in the upper respiratory tract (URT) is common and confounds infection control efforts in the

community. The mean duration of viral RNA detection is ~17 days, and ~14% of people with mild or no symptoms have detectable viral RNA for > 4 weeks. We sought to identify host and immune determinants of prolonged SARS-CoV-2 RNA detection in an intensively-sampled prospective observational cohort of outpatients with mild COVID-19 who had concomitant URT virus and mucosal IgG sampling.

**Methods:** 95 participants ≥ 30 years old with known symptom onset date and at least two positive SARS-CoV-2 qRT-PCR results were enrolled. Participants self-collected mid-nasal, oropharyngeal, and oral crevicular fluid (OCF) samples 4-5 times within 3 weeks. 1-3 months after symptom onset, height and weight were measured and nasopharyngeal, salivary, OCF, and blood samples were collected. SARS-CoV-2 qRT-PCR was performed on samples, and positive samples were tested for propagation in virus culture. A multiplex mucosal IgG immunoassay with multiple SARS-CoV-2 antigens was performed on OCF. Plasma titers of neutralizing antibodies, SARS-CoV-2 spike (S) antibodies, and S-receptor binding domain (RBD) antibodies were obtained by microneutralization assay and indirect ELISA. Time to qRT-PCR clearance was measured from symptom onset until the midpoint between the last positive qRT-PCR test and the next negative test. Associations were estimated using a Cox proportional hazard model. Hazards of viral RNA clearance were compared for different age, sex, race/ethnicity, and body mass index (BMI) groups and whether fever was one of the first three symptoms, adjusting for comorbidities and immunocompromised status.

**Results:** See Table for participant characteristics. Of 56 participants with observed viral RNA clearance, mean time to clearance was 33.5 days. The hazard ratio for obesity vs overweight/normal weight was 0.37 (95% CI 0.18-0.78, p=0.009). Elevated mucosal SARS-CoV-2-specific IgG did not associate with faster viral RNA clearance. The maximum time from symptom onset to virus culture. positive sample was 12 days, which is just after the mean time of first positive mucosal SARS-CoV-2-specific IgG detection.

**Conclusion:** Obesity is associated with prolonged SARS-CoV-2 RNA detection in outpatients. Mucosal SARS-CoV-2 IgG is not associated with faster clearance of viral RNA from the URT, suggesting that viral clearance is mediated by select host immune responses.

|   | Immunocompetent (N=86) | Immunocompromised (N=9) | Overall (N=95)    |
|---|------------------------|-------------------------|-------------------|
| <b>Age at Time of Consent:</b>            |                        |                         |                   |
| Mean (SD)                                 | 56.0 (10.1)            | 56.9 (10.8)             | 56.1 (10.1)       |
| Median [Min, Max]                         | 55.0 [30.0, 79.0]      | 59.0 [41.0, 72.0]       | 56.0 [30.0, 79.0] |
| <b>Sex assigned at birth</b>              |                        |                         |                   |
| Male                                      | 34 (39.5%)             | 5 (55.6%)               | 39 (41.1%)        |
| Female                                    | 52 (60.5%)             | 4 (44.4%)               | 56 (58.9%)        |
| <b>Race/Ethnicity</b>                     |                        |                         |                   |
| Non-Hispanic whites                       | 34 (39.5%)             | 4 (44.4%)               | 38 (40.0%)        |
| African American                          | 33 (38.4%)             | 4 (44.4%)               | 37 (38.9%)        |
| Non-Hispanic other                        | 7 (8.1%)               | 0 (0%)                  | 7 (7.4%)          |
| Hispanic                                  | 12 (14.0%)             | 1 (11.1%)               | 13 (13.7%)        |
| <b>BMI group</b>                          |                        |                         |                   |
| Normal                                    | 16 (18.6%)             | 1 (11.1%)               | 17 (17.9%)        |
| Overweight                                | 25 (29.1%)             | 1 (11.1%)               | 26 (27.4%)        |
| Obese                                     | 45 (52.3%)             | 7 (77.8%)               | 52 (54.7%)        |
| <b>Fever appeared as first 3 symptoms</b> |                        |                         |                   |
| No  | 57 (66.3%)             | 8 (88.9%)               | 65 (68.4%)        |
| Yes                                       | 29 (33.7%)             | 1 (11.1%)               | 30 (31.6%)        |
| <b>Baseline CT value</b>                  |                        |                         |                   |
| Mean (SD)                                 | 19.6 (5.68)            | 20.2 (4.83)             | 19.7 (5.59)       |
| Median [Min, Max]                         | 18.2 [11.9, 33.9]      | 21.4 [13.8, 24.2]       | 18.7 [11.9, 33.9] |
| Missing                                   | 32 (37.2%)             | 5 (55.6%)               | 37 (38.9%)        |
| <b>Comorbidities at baseline</b>          |                        |                         |                   |
| No comorbidities                          | 25 (29.1%)             | 2 (22.2%)               | 27 (28.4%)        |
| Any comorbidities                         | 61 (70.9%)             | 7 (77.8%)               | 68 (71.6%)        |

**210 EARLY CORE SIGNATURE OF SOLUBLE FACTORS IN MILD TO MODERATE SARS-CoV-2 INFECTION**

**Miguel Marin**<sup>1</sup>, Julieta Carabelli<sup>1</sup>, Bibiana Quirant<sup>2</sup>, Dan Ouchi<sup>1</sup>, Aleix Pujol-Gimeno<sup>3</sup>, Oscar Blanch-Lombarte<sup>1</sup>, Ruth Peña<sup>1</sup>, Noemi Lamónja-Vicente<sup>4</sup>, Josep Maria Manresa-Dominguez<sup>4</sup>, Francesc Ramos-Roure<sup>4</sup>, Bonaventura Clotet<sup>4</sup>, Eva Martínez-Caceres<sup>2</sup>, Concepción Violán-Fors<sup>4</sup>, Pere Torán-Monserrat<sup>4</sup>, Julia G. Prado<sup>1</sup>  
<sup>1</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>2</sup>Immunology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, <sup>3</sup>Instituto de Investigación Germans Trias i Pujol, Badalona, Spain, <sup>4</sup>USR Metropolitana Nord. Institut Universitari d'Investigació en Atenció Primària, Barcelona, Spain

**Background:** Understanding the kinetics of early immune responses to SARS-CoV-2 infection is critical to identify potential biomarkers of disease outcome. A myriad of soluble mediators including, pro-inflammatory, immune-suppressors and growth factors, play a relevant role in the disease progression. However, to

date, limited data is available about the role of soluble factors and most studies focus only in severe cases with limited follow-up. Here, we studied with high resolution the kinetics of soluble mediators in mild to moderate cases of SARS-CoV-2 infection 1-90 days from symptom onset (DfSO).

**Methods:** We selected individuals from the ProHEpiC-19 cohort study that included mainly healthcare workers with a PCR+ and mild or moderate disease within 1-14 DfSO. IgG and IgM levels were determined by ELISA. We selected plasma samples (n=30) in the range of 1-90 DfSO, and performed a Luminex multiplex assay including 45 soluble human factors.

**Results:** We identified a core signature including 19 highly correlated soluble factors at 1-14 DfSO, based on clustering analysis. The core signature contained three sub-clusters: #1 (RANTES, IL13, TGf $\alpha$ , PDGF-AB, PDGF-AA, EGF, MIP1b, CD40L and GROb), #2 (G-CSF, PDL1-B7, Fractalkine, IL8, IFN $\gamma$ , Granzyme B and IL10) and #3 (IL7, IL6, and VEGF). We found major changes in #2 and #3 cluster composition between 1-14 and 30-45 DfSO, due to the loss of PDL1-B7, Fractalkine, IL8, IL7, IL6, and VEGF association. Moreover, by 60-75 DfSO, the soluble factor association in #2 and #3 disappeared from the core signature. In addition, we observed a negative correlation between IgG and IgM levels with IL4 production at 1-14 DfSO (IgG:  $\rho = -0.82$ ,  $p = 0.012$ ; IgM  $\rho = -0.83$ ,  $p = 0.011$ ). Similarly, a negative correlation was observed between Igs and Mip3a at 30-45 DfSO (IgG:  $\rho = -0.78$ ,  $p = 0.023$ ; IgM:  $\rho = -0.81$ ,  $p = 0.022$ ).

**Conclusion:** We delineated a core signature of soluble factors in mild to moderate SARS-CoV-2 infection, including growth factors, chemokines and pro-inflammatory cytokines. The longitudinal follow-up of this signature revealed significant changes during the 1-90 DfSO. This information can provide new insights for the definition of biomarkers for patient stratification in mild or moderate SARS-CoV-2 infection. Further data is needed to understand the association between IL4 and Mip3a with low Igs levels.

## 211 FIRST HIGH-DIMENSIONAL EXAMINATION OF INTESTINAL BIOPSIES IN PATIENTS WITH COVID-19

Divya Jha<sup>1</sup>, Ana Gonzalez-Reiche<sup>1</sup>, Teresa Aydilho<sup>1</sup>, Francesca Cossarini<sup>1</sup>, Alexandra E. Livanos<sup>1</sup>, Minami Tokuyama<sup>1</sup>, Brian Lee<sup>1</sup>, Gustavo Martinez-Delgado<sup>1</sup>, Adeb Rahman<sup>1</sup>, Nikhil A. Kumta<sup>1</sup>, Harm Van Bakel<sup>1</sup>, Adolfo Garcia-Sastre<sup>1</sup>, Saurabh Mehandru<sup>1</sup>

<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA

### Background:

SARS-CoV-2, the etiopathological agent for COVID-19, engages host ACE2 receptor for cellular entry. The brush border of the small intestines express high levels of ACE2 in physiological conditions. Gastrointestinal (GI) manifestations are common among COVID-19 patients. However, to date, there is limited information regarding intestinal response to SARS-CoV-2 infection.

### Methods:

Intestinal biopsies were obtained from 17 COVID-19 patients (17.3-17.5 days from the last positive nasal swab) for cellular and transcriptomic analyses using mass cytometry and RNA-sequencing. Ten COVID-uninfected individuals served as controls. The epithelial compartment (EC) and lamina propria (LP) were analyzed separately.

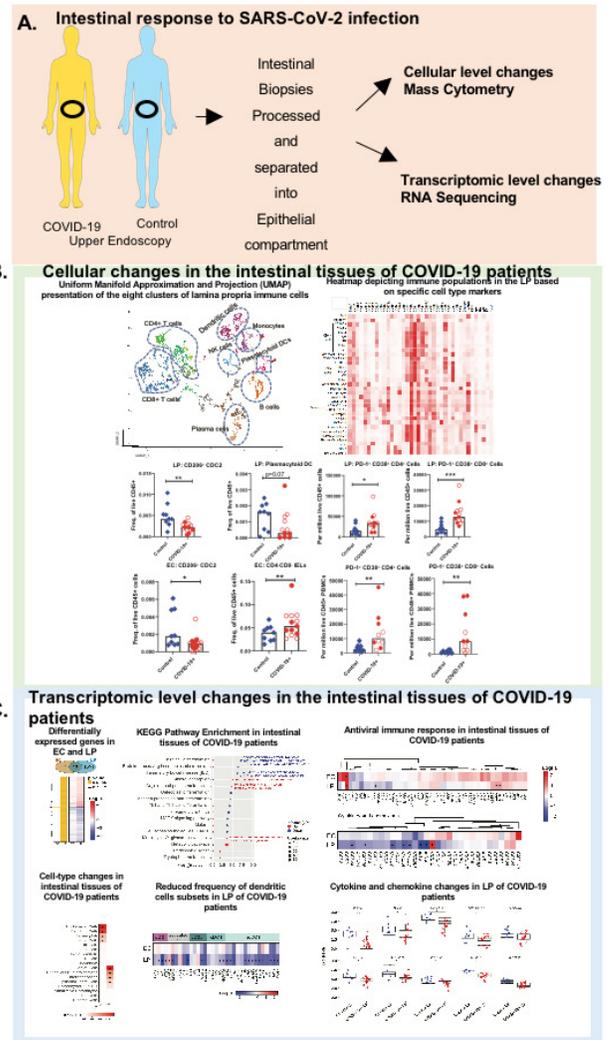
### Results:

The cellular profiles of intestinal tissues from COVID-19 patients showed reduced frequencies of CD206+ CDC2s and plasmacytoid dendritic cells in the LP of COVID-19 patients by mass cytometry. Effector T cell (PD1+CD38+) frequency was increased in the LP and blood of COVID-19 patients. Intraepithelial lymphocytes (IEL) were increased in the EC of COVID-19 patients, with a concomitant decrease in CD206+ CDC2s. RNA sequencing revealed an active downregulation of genes involved in inflammatory pathways including Th17 and IBD-associated pathways, while an upregulation of intestinal barrier function (mucin biosynthesis), amino acid metabolism and mineral absorption pathways was noted. Gene expression of Neuropilin-1 (NRP-1), a putative SARS-CoV-2 receptor as well as key inflammatory cytokines (IL-1\$\$\$ $\alpha$ , IFN-\$\$\$ $\gamma$ , CCL24 and CXCL8) were significantly reduced in COVID-19 patients compared to controls. A low intensity antiviral host response signature was observed predominantly in EC reflecting the cellular localization of the virus.

**Conclusion:** Epithelial, myeloid and lymphoid cell alterations characterize intestinal response to SARS-CoV-2 infection with an unanticipated downregulation of key inflammatory pathways that have been implicated in adverse outcomes associated with COVID-19. These data stand in contrast to reports from the pulmonary and systemic compartments and

identify a potential mitigating role of the GI tract in COVID-19-associated immunopathology.

## First high dimensional examination of intestinal biopsies in patients with COVID-19



The figure shows A. Schema of the methodology adopted for the study.

B. Mass cytometry based cellular analysis: UMAP presentation of immune cell clusters and the heat map presentation of alterations in the markers corresponding to different cell types. Relative frequencies of immune cells in LP, EC and blood of COVID-19 patients. Open red circles denote patients with asymptomatic/mild/moderate disease while filled red circles denote severe COVID-19. All bar plots represent median values. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

C. Sequencing based gene expression changes depicting the distinctness of EC and LP; differential regulation of key pathways, antiviral host response in the intestinal tissues, enrichment and depletion in cellular subsets, depletion of dendritic cell subsets in both EC and LP, and chemokines and cytokines changes in the LP of COVID-19 patients.

## 212 INTESTINAL PERMEABILITY AND MICROBIAL TRANSLOCATION ARE INCREASED IN SEVERE COVID-19

Netanya S. Utay<sup>1</sup>, Jayesh Shah<sup>2</sup>, Anelyna Cantos<sup>2</sup>, Lawrence Purpura<sup>2</sup>, Michael T. Yin<sup>2</sup>

<sup>1</sup>University of Texas Health Science Center at Houston, Houston, TX, USA, <sup>2</sup>Columbia University Medical Center, New York, NY, USA

**Background:** SARS-CoV2 can infect enterocytes, and plasma cells and lymphocytes infiltrate the GI tract. In HIV, increased intestinal permeability and the ensuing microbial translocation are thought to contribute to systemic inflammation. We hypothesize that severe COVID-19 is associated with increased intestinal permeability, leading to microbial translocation and systemic inflammation.

**Methods:** Serum/plasma samples were obtained from participants enrolled in a longitudinal COVID-19 study. Participants had Mild (outpatient), Moderate (inpatient but not requiring Intensive Care Unit (ICU) level care or mechanical ventilation), or Severe (inpatient requiring ICU level care and mechanical ventilation or ECMO) COVID-19. Intestinal fatty acid binding protein (IFABP), lipopolysaccharide binding protein (LBP), and soluble CD14 (sCD14) were

measured by ELISA. Student's t-tests were used for between group comparisons, and paired t-tests were used for within group comparisons.

**Results:** Participants with Moderate and Severe COVID-19 presentations were older compared to the Mild group ( $p < 0.001$ ) (Mild: 42.2 years (range: 20 – 63 years), Moderate: 64.2 years (range: 33 – 97 years); Severe: 61.9 years (range: 32 – 86 years)). The Severe group had a greater proportion of men (69% vs 36%) than women and a greater proportion of black/African Americans (27% vs 6%) than whites versus the Mild group. iFABP, LBP, and sCD14 levels were significantly higher in participants with Moderate or Severe disease compared to Mild disease (Table 1), with no significant differences between Moderate and Severe groups. Among the 65 participants with samples from two timepoints (mean separation of 24.3 +/- 22.4 days), sCD14, iFABP, and LBP did not change significantly.

**Conclusion:** Levels of biomarkers of enterocyte turnover (iFABP), microbial translocation (LBP), and lipopolysaccharide-induced monocyte activation (sCD14) were increased in patients with Moderate and Severe COVID-19 compared to Mild COVID-19. Whether interventions that improve gut health will attenuate the cytokine storm that precipitates Severe COVID-19 needs further study.

| Variable           | Mild         | Moderate     | Severe       | Total        | P Value (Mild vs. Severe) | P Value (Mild vs. Moderate) | P Value (Moderate vs. Severe) |
|--------------------|--------------|--------------|--------------|--------------|---------------------------|-----------------------------|-------------------------------|
| sCD14              |              |              |              |              |                           |                             |                               |
| N                  | 33           | 35           | 72           | 140          |                           |                             |                               |
| -Mean (SD) (ng/mL) | 1799 (573)   | 2245 (633)   | 2426 (584)   | 2233 (642)   | <0.001                    | 0.003                       | 0.161                         |
| i-FABP             |              |              |              |              |                           |                             |                               |
| N                  | 33           | 37           | 75           | 145          |                           |                             |                               |
| -Mean (SD) (ng/mL) | 16.0 (4.4)   | 21.0 (5.4)   | 22.2 (5.5)   | 20.5 (5.8)   | <0.001                    | <0.001                      | 0.291                         |
| LBP                |              |              |              |              |                           |                             |                               |
| N                  | 33           | 37           | 75           | 145          |                           |                             |                               |
| -Mean (SD) (ng/mL) | 34914 (5730) | 38011 (5333) | 40081 (6507) | 38377 (6361) | <0.001                    | 0.023                       | 0.077                         |

## 213 SARS-CoV-2 INFECTS AND REPLICATES IN CELLS OF THE ENDOCRINE AND EXOCRINE PANCREAS

**Janis Müller<sup>1</sup>**, Ruediger Gross<sup>1</sup>, Carina Conzelmann<sup>1</sup>, Jana Krueger<sup>1</sup>, Tatjana Weil<sup>1</sup>, Lennart Koepke<sup>1</sup>, Caterina Prelli Bozzo<sup>1</sup>, Frank Kirchhoff<sup>1</sup>, Konstantin Sparrer<sup>1</sup>, Heiko Lickert<sup>2</sup>, Thomas Barth<sup>1</sup>, Martin Wagner<sup>1</sup>, Sandra Heller<sup>1</sup>, Alexander Kleger<sup>1</sup>, Jan Muench<sup>1</sup>

<sup>1</sup>Ulm University Medical Center, Ulm, Germany, <sup>2</sup>Helmholtz Center Munich, Neuherberg, Germany

**Background:** The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mainly affects the lung, but may also result in extrapulmonary manifestations such as lesions in kidneys, heart, brain, gastrointestinal and endocrine organs. Clinical data suggest that a SARS-CoV-2 infection disturbs glucose homeostasis, and cases of new-onset diabetes mellitus after SARS-CoV-2 infection have been reported. However, experimental evidence that SARS-CoV-2 can infect pancreatic tissue is lacking. We here explored whether pancreatic tissue is susceptible to SARS-CoV-2 infection.

**Methods:** We analyzed healthy human pancreas tissue and cells for ACE2 and TMPRSS2 expression by immunohistochemistry. We exposed human Langerhans islets to SARS-CoV-2 ex vivo and determined viral infection by staining for SARS-CoV-2 spike and nucleoprotein. Viral replication was monitored by detection of released viral RNA by qPCR and infectious titers by TCID50 titration. In addition, infection and the impact of SARS-CoV-2 on cell morphology was examined by electron microscopy. Consequential changes in cell functionality were analyzed by determining insulin secretion and performing transcriptomics. Finally, we performed immunohistochemistry staining of pancreatic sections of four COVID-19 deceased individuals for the presence of SARS-CoV-2 nucleoprotein.

**Results:** Our results show that SARS-CoV-2 infects cells of the human exocrine and endocrine pancreas ex vivo and in vivo. We demonstrate that human  $\beta$ -cells express ACE2 and TMPRSS2, and support SARS-CoV-2 replication. The infection was associated with morphological, transcriptional and functional changes, including reduced numbers of insulin secretory granules in  $\beta$ -cells, upregulation of antiviral gene expression, and impaired glucose-stimulated insulin secretion. Finally, all four analyzed full body autopsies of COVID-19 patients showed SARS-CoV-2 nucleoprotein in pancreatic cells, including those that stain positive for the  $\beta$ -cell marker NKX6.1.

214



## UNIQUE CARDIOMETABOLIC IMMUNE SIGNATURES IN SEVERE-COVID-19 PATIENTS AND SURVIVORS

**Namal Liyanage<sup>1</sup>**, Manuja Gunasena<sup>1</sup>, Yasasvi Wijewantha<sup>1</sup>, Emily Bowman<sup>1</sup>, Janelle Gabriel<sup>1</sup>, Amrendra Kumar<sup>1</sup>, Aaren Kettelhut<sup>1</sup>, Anushka Ruwanpathirana<sup>1</sup>, Krishanthi Weragalaarachchi<sup>1</sup>, Dhanuja Kasturiratna<sup>2</sup>, Anna Vilgelm<sup>1</sup>, Joseph Bednash<sup>1</sup>, Thorsten Demberg<sup>3</sup>, Nicholas Funderburg<sup>1</sup>

<sup>1</sup>The Ohio State University, Columbus, OH, USA, <sup>2</sup>Northern Kentucky University, Highland Heights, KY, USA, <sup>3</sup>Marker Therapeutics, Inc, Houston, TX, USA

**Background:** Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly pathogenic corona virus which causes COVID-19 and resulted in millions of deaths and led to a global public health emergency. SARS-CoV-2 infected patients exhibit a wide variety of clinical manifestations ranging from asymptomatic to severe complications and death. SARS-CoV-2 infection can lead to excessive immune activation, inflammation and multi-organ damage. Clinical data showed that COVID-19 may promote the development of cardiovascular disorders (CVDs). Immune activation, thrombosis, cytokine storm, and altered adhesion molecule expression on leukocyte populations, have been proposed as possible mechanisms that trigger COVID-19 associated CVDs. A lack of systematic studies on how SARS-CoV-2 infection triggered immune responses that may lead to CVDs, hinder early risk identification and therapeutic interventions.

**Methods:** In this study, by using deep immune cell profiling (high dimensional flowcytometry) in fresh whole blood and extensive plasma cytokine and chemokine profiling, we explore potential mechanisms that could lead to CVDs in severe COVID-19 patients that did not have previous known CVDs (ICU) (n=20) as well as patients recovered from COVID-19 (RD) (n=30) compared to healthy donors (n=17). To identify the major statistically significant immune signatures that predict CVD risk in ICU patients and RD, we performed parametric (ANOVA) and non-parametric (Kruskal-Wallis) statistical tests with Dunn's and Tukey's post hoc tests. Integrative correlation and network analysis were performed by computing Spearman's coefficients. Correlations with  $r > 0.3$ ,  $r < -0.3$  and  $P < 0.01$  were considered significant.

**Results:** We found that significantly elevated eosinophils, neutrophils and increased circulating levels of tissue factor, fatty acid binding protein 4 and, LPS binding protein in ICU patients suggested increased immune activation and thrombotic risk. Interestingly, we found significant elevation of several immune parameters (TIMP-1, TIMP-2, M-CSF, Monocytes) that were associated with cardiometabolic risk, even 3-4 months after the recovery of initial COVID-19 infection in RD. Furthermore, we found unique relationship with cytokine and cellular responses in ICU and RD groups compare with HD.

**Conclusion:** Our data strongly suggest a possible mechanistic link between SARS-CoV-2 induced dysregulated immune responses and increased cardiometabolic risk in severe COVID-19 patients.

## 215 IL10 AND B CELLS COOPERATE TO PREDICT SARS-CoV-2 DISEASE SEVERITY

**Susan Pereira Ribeiro<sup>1</sup>**, Jozefina De Clercq<sup>2</sup>, Ruth Seurinck<sup>2</sup>, Niels Vandamme<sup>2</sup>, Linyong Mao<sup>1</sup>, Ashish A. Sharma<sup>1</sup>, Adam N. Pelletier<sup>1</sup>, Basiel Cole<sup>2</sup>, Marion Pardons<sup>2</sup>, Sarah Gerlo<sup>2</sup>, Anna Bruchez<sup>3</sup>, Robert Balderas<sup>4</sup>, Martin Guilliams<sup>2</sup>, Linos Vandekerckhove<sup>2</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Ghent University, Ghent, Belgium, <sup>3</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>4</sup>BD Biosciences, San Francisco, CA, USA

**Background:** SARS-COV2 has infected more than 62 million people world-wide and led to almost 1.5 million deaths. Exacerbated inflammation, lymphopenia and coagulopathy are part of the complex cascade of events that can lead to death. Additionally, elevated B cells, antibody production and heightened IL-10 levels were associated with severe disease.

**Methods:** We performed scRNAseq/CITEseq on matched peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage (BAL) from 5 COVID-19 positive donors with different disease outcomes at time of hospitalization. B cell gene signatures and cytokine/chemokine levels in plasma and BAL fluid (BALF) were associated to live neutralizing antibodies (NAbs) as well as to viral load (VL) readouts.

**Results:** Fourteen clusters of B cells were identified in PBMCs. They included subsets of naive, memory B cells and plasmablasts. Ten clusters, comprising

mature/effector B cells, were found in BAL while no naïve B cells were observed. Titers of NABs in the BALF were significantly associated to memory B cell frequencies and were inversely correlated to VL. Systemic NABs reflected Nabs titers in the BALF, supporting that antibody production in the site of infection impacted the circulating levels of Abs. Peripheral B cells were enriched in signatures associated to chemokine signaling which was positively correlated to the chemokines measured in BALF. This suggests that mature B cells in PBMCs could migrate from periphery to the lung to counteract infection. Importantly, B cells in COVID-19 patients presented a strong inflammatory signature that included heightened levels of interferons and IL-10 signaling, the latter a marker of disease severity known to promote B cell differentiation and antibody production.

**Conclusion:** While this work corroborates prior findings in the literature, it associates IL10 levels and B cell migration to disease severity. A detailed analysis of the antibody repertoire and B cell clonality induced upon infection is under way and would support the understanding of the role of B cells in SARS-CoV-2 pathogenesis and also lead to possible immune interventions to counteract severity.

## 216 RECRUITMENT OF SPECIFIC MONOCYTE AND DC SUBSETS TO THE LUNG DURING SEVERE COVID-19

**Ildefonso S. Cerrillo**<sup>1</sup>, Pedro Landete<sup>1</sup>, Ignacio De Los Santos<sup>1</sup>, Hortensia De La Fuente<sup>1</sup>, Maria J. Calzada<sup>1</sup>, Isidoro Gonzalez<sup>1</sup>, Arantazu Alfranca<sup>1</sup>, Francisco Sanchez<sup>2</sup>, Cecilia Muñoz<sup>1</sup>, Joan Soriano<sup>1</sup>, Julio Ancochea<sup>1</sup>, Enrique Martin-Gayo<sup>2</sup>, for the REINMUN COVID Research Group

<sup>1</sup>Hospital Universitario de La Princesa, Madrid, Spain, <sup>2</sup>Universidad Autónoma de Madrid, Madrid, Spain

**Background:** SARS-CoV-2 is responsible for the development of COVID-19 in infected individuals, who can exhibit mild to severe symptoms including acute respiratory distress syndrome (ARDS). Critical patients developing ARDS are characterized by exacerbated inflammation and dysregulated adaptive immune responses. However, the differential association of specific myeloid subsets of dendritic cells (DC) and monocytes (Mo) to the induction of ARDS in these critical COVID-19 patients is poorly understood.

**Methods:** A total of 64 COVID-19 patients qPCR positive for SARS-CoV were included in the study. Patients were stratified into 3 subgroups attending to non-severe (G1), severe (G2) and critical (G3) severity based on changes in respiratory frequency (RF), partial pressure arterial oxygen and fraction of inspired oxygen ratio (PaO<sub>2</sub>/FiO<sub>2</sub>) and respiratory failure values. PBMC were obtained from blood samples collected from all COVID-19 patient subgroups and with paired cell infiltrates from bronchial aspirates in the case of critical G3 patients requiring respiratory support. PBMC samples from n=22 non-COVID individuals were also included for comparison purposes. Expression of markers defining different DC and Mo subsets and their level of activation were analyzed by multicolor flow cytometry.

**Results:** CD141+ conventional and CD123hi plasmacytoid DCs were similarly depleted from blood in COVID-19 patients (p<0.0001; p<0.0001) from all severity subgroups but were absent in the lung infiltrates from critical individuals. In contrast, CD1c+ DC, inflammatory transitional and non-classical Mo were dramatically depleted from the blood and preferentially enriched in lung infiltrates in patients with critical G3 COVID-19 individuals (p<0.01; p<0.001; p<0.001). Remarkably, proportions of transitional Mo in the blood were increased in G1 COVID-19 patients exhibiting non-severe progression. Importantly, myeloid subsets infiltrating the lung of critical G3 COVID-19 patients were characterized by increased expression of the activation marker CD40. Moreover, activated CD38+ CXCR5+ and CD38+ CXCR5- CD8+ T cells were enriched in the lungs from critical COVID-19 patients (p<0.001; p<0.05). Finally, higher levels of CD40 on transitional Mo were positively associated with proportions of CD38+ CXCR5- CD8+ T cells in the lung.

**Conclusion:** The study identified the recruitment of specific myeloid subsets from the blood to the lung in critical COVID-19 patient that could be targeted by future therapies.

## 217 SARS-CoV-2 ORF3a ACTIVATES THE NLRP3 INFLAMMASOME

**Kimberly E. Rousseau**<sup>1</sup>, Alexis Figueroa<sup>1</sup>, Guido Massaccesi<sup>1</sup>, Michael Chattergoon<sup>1</sup>

<sup>1</sup>Johns Hopkins University, Baltimore, MD, USA

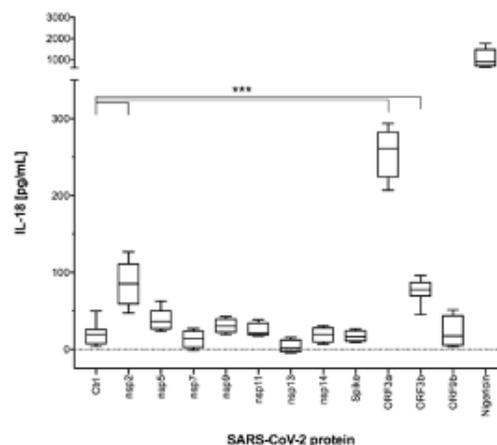
**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of Coronavirus Disease 2019 (COVID-19), began circulating

in humans in late 2019 and has since spread to pandemic levels. Numerous clinical studies into the inflammatory syndrome in critically ill COVID-19 patients have highlighted aberrant immune responses and levels of pro-inflammatory cytokines. Among the dysregulated pro-inflammatory cytokines are interleukin (IL)-18 and IL-1 $\beta$ . These two cytokines are produced after the activation and assembly of inflammasomes, multi-protein structures of the innate immune system that recognize and respond to traumas such as viral infection, tissue damage, and other stimuli. The purpose of this study is to define the viral trigger for inflammasome activation by SARS-CoV-2 and to understand its mechanism for activation.

**Methods:** In this study, we employed a transfection reconstitution system to study the structural and non-structural components of SARS-CoV-2 for inflammasome activation. Plasmids encoding the inflammasome components and individual plasmids encoding each SARS-CoV-2 protein of interest were co-transfected, allowing us to probe the relationship between these viral proteins and the NLRP3 inflammasome.

**Results:** We report that the accessory protein open reading frame (ORF) 3a is sufficient to trigger assembly of the NLRP3 inflammasome and production of mature IL-18. Among the 26 viral proteins assayed, non-structural protein (nsp) 2 and ORF3b also triggered NLRP3 inflammasome activity and release of mature IL-18, though to a less extent. MCC950, a selective small molecule inhibitor of the ATPase function of NLRP3, reduces IL-18 production in response to these viral proteins to mock levels.

**Conclusion:** The identification of SARS-CoV-2 ORF3a as the viral protein responsible for NLRP3 inflammasome activation is an important step in understanding the inflammatory response seen in severe COVID-19 disease. Further study into the mechanism of this event has the potential to highlight clinical targets for drug interventions in severe cases of the disease.



SARS-CoV-2 ORF3a, nsp2, and ORF3b initiate the assembly of the NLRP3 inflammasome. Nigericin treatment at 5  $\mu$ M. Ctrl represents eGFP control plasmid. Data are from 2 or more independent experiments with n  $\geq$  4. Box showing 25<sup>th</sup> and 75<sup>th</sup> percentiles; whiskers showing 5<sup>th</sup> and 95<sup>th</sup> percentiles. \*\*\* p  $\leq$  0.001 (One-way ANOVA, Tukey HSD).

## 218 COLONIC GRANZYME B+ CD4 T CELLS ASSOCIATE WITH GUT AND SYSTEMIC T-CELL ACTIVATION

**Stephanie Dillon**<sup>1</sup>, Emily Cooper<sup>1</sup>, Tezha Thompson<sup>1</sup>, Kaylee Mickens<sup>1</sup>, Kejun Guo<sup>1</sup>, Cheyret Wood<sup>1</sup>, Katerina Kechris<sup>1</sup>, Mario Santiago<sup>1</sup>, Cara Wilson<sup>1</sup>

<sup>1</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA

**Background:** Alterations in gut homeostasis and changes in the microbiome (dysbiosis) have been linked to features of pathogenesis and comorbidity events in people with HIV (PWH). We reported human gut lamina propria (LP) CD4 T cells express the cytolytic molecule Granzyme B (GZB) following in vitro exposure to commensal enteric bacteria with enhanced expression in the presence of HIV-1. Here, we investigated CD4 T cell GZB expression in PWH and uninfected controls and explored its relationship with in vivo markers of HIV-1 pathogenesis and gut microbiome.

**Methods:** GZB+ CD8- (due to downregulation of CD4 by HIV-1) T cells were enumerated in archived colon tissue (PMID24399150) from 10 untreated, chronically-infected PWH and 10 uninfected controls using multispectral imaging. GZB+ CD4 T cells in donor-matched peripheral blood (PB) CD4 T cells were measured using flow cytometry. All participants gave informed consent. Comparisons between groups were performed using Mann-Whitney U tests.

Associations between GZB+ T cells and measures of systemic inflammation, immune activation, microbial translocation, colon T cell and dendritic cell frequencies and activation and relative abundance (RA) of mucosa-associated bacteria altered in PWH, were performed using linear models adjusted for age, sex, HIV-1 status and corrected for multiple comparisons.

**Results:** The number of LP GZB+ CD4 T cells per tissue area were higher in PWH (median 39 GZB+ CD8- T cells/mm<sup>2</sup>, range 16-104) versus controls (17, 6-33; P=0.005) despite relative depletion of CD4 T cells (PWH: 400 CD8- T cells/mm<sup>2</sup>, 226-622; controls: 930, 517-1090; P<0.001). Numbers of LP GZB+ CD4 T cells were significantly associated with increasing PB and colon CD4 and CD8 T cell activation levels and RA of Prevotella species (Table 1). Percentages of PB CD4 T cells expressing GZB were higher in PWH (8.7%, 0.8-15.1) versus controls (0.4%, 0.01-3.8; P=0.0006). By contrast, PB GZB+ CD4 T cells did not associate with systemic or colon measurements or with microbiota RA.

**Conclusion:** GZB+ CD4 T cells are enriched in colon tissue of untreated PWH. Colon, but not PB, GZB+ CD4 T cells, associated with colon and systemic T cell activation, a predictor of disease progression, and with increasing RA of Prevotella species, commensal enteric bacteria previously linked to mucosal inflammation and T cell activation. These novel findings implicate GZB+ CD4 T cells as potential key players in HIV-associated gut immune activation, processes potentially driven by dysbiotic bacteria.

**Table 1. Linear models with number of colonic GZB+ CD4 T cells as the outcome.**

| Predictor (representing a different model fit)              | Regression Slope Estimate (SE) | FDR*   |
|---|--------------------------------|--------|
| <b>Blood T cell activation</b>                              |                                |        |
| CD38+ HLA-DR+ CD4 T cells (% of CD4 T cells)                | 16.3 (4.4)                     | 0.02   |
| CD38+ HLA-DR+ CD8 T cells (% of CD8 T cells)                | 2.8 (0.8)                      | 0.02   |
| <b>Colonic T cell activation</b>                            |                                |        |
| CD38+ HLA-DR+ CD4 T cells (#/g tissue)                      | 0.0002 (0.0004)                | 0.0004 |
| CD38+ HLA-DR+ CD8 T cells (#/g tissue)                      | 0.00006 (0.00001)              | 0.002  |
| <b>Mucosa-associated bacteria</b>                           |                                |        |
| RA of Prevotella (% of total bacteria)                      | 76.4 (16.8)                    | 0.01   |
| RA of <i>Prevotella stercorea</i> (% of classified species) | 249.3 (75.0)                   | 0.03   |
| RA of <i>Prevotella copri</i> (% of classified species)     | 79.5 (22.1)                    | 0.02   |

\*False Discovery Rate correcting for multiple comparisons. Microbiome variables (N=32) were assessed and corrected for separately from other markers of HIV-1 pathogenesis (N=21). SE: Standard Error. RA: relative abundance.

**219 ALTERED GASTROINTESTINAL PLASMA CELLS CONTRIBUTE TO DYSBIOSIS AND VIRAL REPLICATION**

**Francesca Cossarini<sup>1</sup>, Louise Leyre<sup>1</sup>, Divya Jha<sup>1</sup>, Minami Tokuyama<sup>1</sup>, Alexandra E. Livanos<sup>1</sup>, Michael Tankelevich<sup>1</sup>, Gustavo Martinez-Delgado<sup>1</sup>, Adam Z. Horowitz<sup>1</sup>, Ilaria Mogno<sup>1</sup>, Ivo Sahbandar<sup>2</sup>, Michael Cruz<sup>1</sup>, Judith A. Aberg<sup>1</sup>, Lishomwa Ndhlovu<sup>2</sup>, Jeremiah J. Faith<sup>1</sup>, Saurabh Mehandru<sup>1</sup>**  
<sup>1</sup>*Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>2</sup>Weill Cornell Medicine, New York, NY, USA*

**Background:** Intestinal dysbiosis is a feature of HIV-1 infection. Secretory IgA mediate critical bidirectional interactions between the mucosal immune system and the intestinal microbiome. Here, we sought to better define the role played by mucosal IgA in mediating dysbiosis during chronic HIV-1 infection.

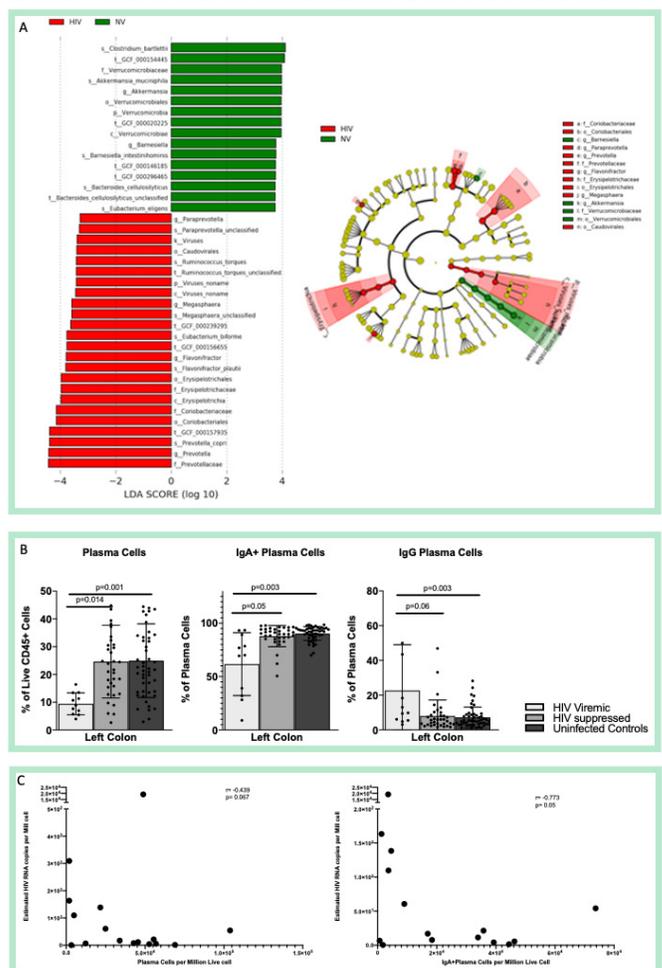
**Methods:** 11 HIV-infected viremic patients, 35 HIV-infected patients with suppressed viremia and 50 HIV-uninfected healthy controls were recruited to undergo ileocolonoscopy. Mucosal mononuclear cells were obtained using collagenase digestion of fresh biopsies. B cell subsets including plasma cells (PC) (defined as CD38highCD27+CD45+ live cells) were examined by multiparameter flow cytometry. Paraffin-preserved biopsy samples were examined via fluorescent microscopy co-staining IgA, CD138 and DAPI. Metagenomic sequencing of stool DNA was performed using Illumina HiSeq. The relative abundance of each microbe was obtained by metaphlan with differences in taxonomic composition across groups determined by LEfSE. HIV RNA was quantified from cryo-preserved mucosal biopsies using qRT-PCR.

**Results:** Stool metagenomic sequencing revealed, amongst other differences, higher relative abundance of Prevotellaceae (p=0.009) and viruses (p=0.027) in HIV-infected subjects and higher relative abundance of Bacteroides cellulosilyticus (p=0.01) and Akkermansia muciniphila (p=0.005) in HIV-uninfected controls. Significantly lower frequency of PC was observed in the colon of HIV-infected viremic patients, compared both to aviremic HIV patients and to uninfected controls [median (IQR) 8.8% of CD45+ Cells (5.7-13.4) vs 23.9 (15.4-32.3) vs 22.4 (18.8-34.1), p=0.014 and p=0.001]. Within PC subsets, IgA+ PC were reduced in viremic HIV subjects [70% of total PC (32-89.2)] compared to controls [92.2% of total PC (87.2-94.9), p=0.003]; while IgG+ PC were significantly increased in viremic HIV subjects [9.7 (5.5-43.5)] compared to HIV uninfected controls [5.2 (3.2-8.8), p=0.032]. Fluorescent microscopy confirmed a trend towards lower frequencies of PC in the left colon per high power field

in viremic HIV subjects [115 (82.2-283)] compared to controls [291.3 (230.4-360.1), p=0.09]. Similar trends in PCs were seen in the terminal ileum. Finally, HIV-RNA levels in the ileum inversely correlated with the frequency of IgA+ PC (Spearman's r=-0.773, p=0.05).

**Conclusion:** Depletion of IgA+ PC of viremic HIV patients might contribute to intestinal dysbiosis and is associated with higher tissue levels of HIV RNA.

**ALTERED GASTROINTESTINAL PLASMA CELLS CONTRIBUTE TO DYSBIOSIS AND VIRAL REPLICATION**



Panel A: LEfSE analysis and dotgram of stool microbes relative abundances in HIV-infected subjects and uninfected controls. Panel B: Frequency of Plasma Cells and subclasses of Plasma Cells across groups. Bars represent median (IQR) range. Comparisons between groups were performed with Wilcoxon rank test. Panel C: Correlation between gastrointestinal HIV RNA levels and (left panel) Plasma Cells and (right panel) IgA+ Plasma Cells at the Terminal Ileum site. Spearman's r values are reported

**220 HIV REBOUND IN CONTROLLERS IS ASSOCIATED WITH SPECIFIC FECAL MICROBIOME PROFILE**

**Yanhui Cai<sup>1</sup>, Steven G. Deeks<sup>2</sup>, Cynthia Brinson<sup>3</sup>, Moti Ramgopal<sup>4</sup>, Norman Jones<sup>5</sup>, Edwin DeJesus<sup>5</sup>, Anthony Mills<sup>6</sup>, Peter Shalit<sup>7</sup>, Brian Moldt<sup>1</sup>, Liao Zhang<sup>1</sup>, Elena Vendrame<sup>1</sup>, Devi SenGupta<sup>1</sup>, Diana Brainard<sup>1</sup>, Jeffrey Wallin<sup>1</sup>, Ondrej Podlaha<sup>1</sup>**  
<sup>1</sup>*Gilead Sciences, Inc, Foster City, CA, USA, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA, <sup>3</sup>Central Texas Clinical Research, Austin, TX, USA, <sup>4</sup>Midway Immunology and Research Center, Fort Pierce, FL, USA, <sup>5</sup>Orlando Immunology Center, Orlando, FL, USA, <sup>6</sup>Mens Health Foundation, West Hollywood, CA, USA, <sup>7</sup>Peter Shalit MD and Associates, Seattle, WA, USA*

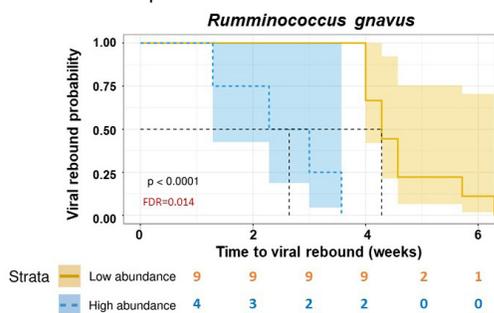
**Background:** HIV infection negatively impacts gut immune homeostasis and frequently leads to dysbiosis which can only be partially restored by antiretroviral therapy (ART) in people with HIV (PWH). In a placebo-controlled Phase 1b trial, vesatolimod (VES), an oral TLR7 agonist, was shown to increase interferon stimulated genes (ISGs), immune cell activation, and modestly delay viral rebound after ART interruption in HIV virologic controllers (VC). We investigated the fecal microbiome dynamics and association with virologic outcome in this trial.

**Methods:** We enrolled 25 VC (pre-ART viral load 50-5000 c/mL) on ART. Seventeen participants received 10 biweekly VES doses, and 8 received placebo prior to an analytical treatment interruption (ATI). Fecal samples from male

participants were assessed at baseline and 2 weeks after the 10th dose for microbial abundance and diversity evaluation. Feces from an additional 14 male healthy volunteers and 9 male ART-suppressed chronic HIV infected participants (CHI) were included to assess baseline differences due to HIV infection by Wilcoxon test. Associations between immune biomarkers and bacterial abundance at the phylum level were measured by Spearman's rank correlation. A univariate Cox Proportional Hazard regression model explored the association between time to viral rebound and the abundance of microbiota species.

**Results:** *Prevotella copri* was enriched in VC at baseline ( $p=0.0018$ ), as well as in CHI ( $p=0.0024$ ), compared to healthy volunteers. VES partially reversed this dysbiosis by decreasing *Prevotella copri* levels closer to those in healthy volunteers. Proteobacteria abundance was positively correlated with VES-induced elevation of ISGs and Ki67+CD4+ T cells ( $r=0.75$ ,  $p=0.01$ ). Higher abundance of fecal *Ruminococcus gnavus* at the pre-ATI timepoint was associated with shorter time to viral rebound after ATI in the overall study population (FDR adjusted  $p$ -value=0.014).

**Conclusion:** The enrichment of certain microbiome species may contribute to HIV persistence, as evidenced by faster rebound off ART. VES enhances the immune response and can potentially favorably alter the composition of the fecal microbiome. Further studies are needed to understand the mechanistic interactions between immune modulation and microbiome, and subsequent impacts on antiviral responses and HIV reservoir in cure studies.



## 221 GUT MICROBIAL DYSBIOSIS PRECEDES HIV WITH LIMITED CHANGES AFTER SEROCONVERSION

**Jennifer A. Fulcher**<sup>1</sup>, Fan Li<sup>1</sup>, Nicole Tobin<sup>1</sup>, Sara Zabih<sup>1</sup>, India Richter<sup>1</sup>, Amy Ragsdale<sup>1</sup>, Jesse Clark<sup>1</sup>, Richard T. D'Aquila<sup>2</sup>, Brian Mustanski<sup>2</sup>, Michele Kipke<sup>3</sup>, Steve Shoptaw<sup>1</sup>, Pamina M. Gorbach<sup>1</sup>, Grace M. Aldrovandi<sup>1</sup>

<sup>1</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>2</sup>Northwestern University, Chicago, IL, USA, <sup>3</sup>Children's Hospital Los Angeles, Los Angeles, CA, USA

**Background:** Alterations in the gut microbiome have been associated with HIV infection. However, the relative impact of HIV versus other confounders has been difficult to determine in cross-sectional studies. To address this, we sought to examine the gut microbiome longitudinally within individuals before and after HIV seroconversion.

**Methods:** We used rectal swabs collected from 27 sexual minority men before and after HIV acquisition for microbiome analysis using shotgun metagenomic sequencing. Samples were obtained from ongoing cohort studies in Los Angeles (mSTUDY, HYM), Chicago (RADAR), and Lima, Peru collected from 2014 to 2018. Pre-infection samples ranged from 3 to 12 months prior to first positive HIV test, and post-infection samples ranged from 3 to 18 months after first positive HIV test. For comparison, a control cohort was created using rectal swabs from 28 individuals without HIV over the same time period from the Los Angeles (mSTUDY) and Lima, Peru cohorts. Control samples were matched on age, race/ethnicity, BMI, substance use, and receptive anal intercourse frequency/partners. Generalized linear mixed models were used to identify significant differences before and after HIV infection as well as between pre-HIV cases and controls.

**Results:** Microbiome composition was compared within cases ( $n=27$ ) before and after HIV infection, and also compared between cases and controls ( $n=28$ ). Race/ethnicity and geography ( $p<0.001$ ), but not HIV serostatus ( $p=0.61$ ), were significant drivers of microbiome variation. The only significant changes in the microbiome following HIV infection were increased *Fusobacterium mortiferum* and decreased *Dysosmobacter welbionis*. These changes persisted even when controlling for antiretroviral therapy. The greatest differences in microbiome composition were seen between pre-HIV infection visits compared to controls.

Participants who acquired HIV had pre-existing alterations in microbiome composition with decreased *Bacteroides AT1C1*, *Bacteroides uniformis*, *Bacteroides caccae*, *Ruminococcus bicirculans*, and *Anaerostipes hadrus*.

**Conclusion:** Longitudinal sampling showed specific alterations in the gut microbiome in the first year following HIV acquisition, and also identified pre-existing differences in participants who acquired HIV compared to matched control participants observed over the same period. These data highlight the importance of understanding the role of the microbiome in both HIV susceptibility and disease.

## 222 A RANDOMIZED CONTROLLED TRIAL OF RIFAXIMIN IN INDIVIDUALS WITH HIV ON LONG-TERM ART

**Kristi Huik**<sup>1</sup>, James Q. Virga<sup>1</sup>, Catherine Rehm<sup>2</sup>, Jennifer Bell<sup>1</sup>, Brian Luke<sup>3</sup>, Netanya S. Utay<sup>4</sup>, Deborah McMahon<sup>5</sup>, Anuradha Ganesan<sup>6</sup>, Frank Maldarelli<sup>1</sup>

<sup>1</sup>National Cancer Institute, Frederick, MD, USA, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>3</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA, <sup>4</sup>University of Texas Health Science Center at Houston, Houston, TX, USA, <sup>5</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>6</sup>Uniformed Services University of the Health Sciences, Bethesda, MD, USA

**Background:** Ongoing immune activation plays a key role in clinical outcomes of people living with HIV during long-term combination antiretroviral therapy (cART); the forces responsible for elevated immune activation (IA) remain uncertain. Microbial translocation from the gastrointestinal tract have been reported to contribute to immune activation, and a modest reduction of IA with use of the nonabsorbable antibiotic Rifaximin in immune nonresponders, presumably by decreasing microbial translocation across the gut. However, the effects of Rifaximin on the gut microbiome in HIV infected individuals remain uncertain. We recently conducted a randomized placebo-controlled trial of the effects of Rifaximin on IA in individuals with HIV undergoing cART. Here we report analysis of the gut microbiome during Rifaximin therapy and analyze the bacterial composition of stool obtained during the course of the study.

**Methods:** Individuals ( $N=42$ ) receiving cART >3 years with HIV viremia <50 c/ml were enrolled in a placebo-controlled double blind crossover study of Rifaximin. A panel of soluble and cellular markers of IA were measured throughout the study; the primary endpoint was the change in sCD14 levels during the placebo and Rifaximin phases of the study. In addition, stool samples were obtained throughout the study and microbial communities were assessed based on 16s rRNA gene amplicon sequencing of day 0 and day 28 stool samples of each arm. Standard measures of microbial diversity, operational taxonomic units (OTUs) and Shannon entropy were determined, and the log ratios of these determinations on day 0 and day 28 were compared using Wilcoxon rank sum tests.

**Results:** 17 participants provided samples at the beginning and end of each phase; participants (10% female, 22% non-white) had median age 49 years, with a median duration of HIV infection of 20 years and entry CD4=302 cells/ $\mu$ l. Microbial communities were recovered from stool samples and 25,000 reads were available for analysis per sample. As expected, Firmicutes and Bacteroidetes phyla accounted for up to 90% of the microbial composition in each participant. A modest but significant decrease in OTUs ( $p=0.04$ ) was detected in the Rifaximin arm of the study; no significant changes in Shannon entropy were detected.

**Conclusion:** Short-term Rifaximin therapy resulted in modest but significant change in the gut microbiome, but this shift did not result in downstream changes in IA.

## 223 TRANSMISSION OF ATTENUATED HIV-1 FROM A CHRONIC PROGRESSOR TO A VIREMIC CONTROLLER

**Bezawit A. Woldemeskel**<sup>1</sup>, Caroline C. Garliss<sup>1</sup>, Joseph Cofrancesco<sup>1</sup>, Joel Blankson<sup>1</sup>

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Viremic controllers (VC) are individuals who maintain low viral loads without anti-retroviral therapy and are considered models of functional cure. Characterizing the mechanisms that lead to the natural control of HIV-1 is needed to better understand and inform cure strategies. In this study, we analyze an HIV-1 transmission pair, where a chronic progressor (TP5M) transmitted HIV-1 to a recipient who became a VC (TP5F).

**Methods:** We sequenced replication competent virus to assess genome integrity. Virus replication was tested in-vitro by a growth kinetics assay utilizing a p24 ELISA. In-vivo replication was assessed by infecting CD4 T cell

engrafted Nod SCID Gamma humanized mice. Further, the ability of viruses to downregulate HLA-A2 and CD4 in infected cells was assessed by flow cytometry. **Results:** The chronic progressor (TP5M) had a CD4 count of 76 cells/μL and a viral load of 673,000 copies/mL, while the VC (TP5F) had a CD4 count of 964 cells/μL and a viral load of 62 copies/mL. Neither patient had protective HLA alleles. Replication-competent isolates from both subjects were obtained with a viral outgrowth assay. The isolate from TP5M replicated slightly better than an isolate from TP5F with p24 concentrations of 1441 ng/ml versus 655 ng/ml at day 10 compared to 44 ng/ml versus 23 ng/ml at day 0. The viral isolate from TP5M replicated better than the isolate from TP5F in humanized mice with viral loads of 1.4e8 and 3.7e6 copies/ml versus 9.6e6 and 2.5e4 copies/ml respectively at 7 days post-infection. Sequencing of LTR, gag, pol, integrase and the accessory genes confirmed that TP5F and TP5M were a transmission pair. All four TP5F replication-competent viral isolates had numerous mutations and deletions in nef, including a 16 base pair deletion that resulted in a frame shift and premature stop codon. These mutations affected nef function as primary CD4+ T cells infected with TP5F virus had 2-to-4-fold lower downregulation of CD4 and HLA-A2 (mean fluorescence intensity [MFI] of 9664 and 3083) compared to TP5M virus infected cells (MFI of 3634 and 782 respectively). **Conclusion:** Together, these data suggest that unlike TP5M, TP5F viral isolates are attenuated due to non-functional nef. This attenuation probably contributed to the natural control of viral replication in TP5F. Our data suggests that transmission of attenuated minor variants can explain discordant outcomes in some transmission pairs.

## 224 A META GENOME-WIDE ASSOCIATION STUDY OF HIV-DISEASE PROGRESSION IN HIV CONTROLLERS

**Luis M Real**<sup>1</sup>, María Sáez<sup>2</sup>, Anaïs Corma-Gomez<sup>1</sup>, Antonio Gonzalez-Perez<sup>3</sup>, Christian A. Thorball<sup>4</sup>, Rocio Ruiz<sup>5</sup>, Reyes Jiemenez-Leon<sup>6</sup>, Alejandro Gonzalez-Serna<sup>1</sup>, María C. Gasca-Capote<sup>6</sup>, Alberto Perez-Gomez<sup>6</sup>, Jacques Fellay<sup>4</sup>, Mathias Lichterfeld<sup>7</sup>, Ezequiel Ruiz-Mateos<sup>6</sup>, for the Swiss HIV Cohort Study <sup>1</sup>Hospital Universitario de Valme, Seville, Spain, <sup>2</sup>Centro de Biología Molecular Severo Ochoa, Madrid, Spain, <sup>3</sup>Centro Andaluz de Estudios Bioinformáticos, Seville, Spain, <sup>4</sup>School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, <sup>5</sup>Facultad de Farmacia, Universidad de Sevilla, Seville, Spain, <sup>6</sup>Institute of Biomedicine of Seville, Sevilla, Spain, <sup>7</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

### Background:

HIV-controllers are a heterogeneous group of individuals who maintain low or undetectable levels of viremia in the absence of antiretroviral treatment. Some of them eventually experience immunologic progression with marked CD4+ T-cell decline. Our aim was to identify genetic factors associated with avoiding CD4+ T-cell loss in HIV-controllers.

### Methods:

Retrospective case-control genome wide association study (GWAS). We analyzed genotype data-sets within long-term non-progressor HIV-1 controllers (LTNP-Cs); who maintained CD4+ T-cells counts >500 cells/mm<sup>3</sup> for more than 7 years after HIV-1 diagnosis vs non-LTNP-Cs who developed CD4+ T-cell counts <500 cells/mm<sup>3</sup>, belonging to both, the International HIV-controllers Study Cohort (ICSC) and Swiss HIV Cohort Study (SHCS). Plink was used to carry out individual GWAS and meta-GWAS, logistic regression procedures and fixed or random effect models were applied, respectively. Magma and Webgestalt softwares were used to carry out gene-based association studies with detection of multi-marker effects and enrichment analyses with multiple testing corrections, respectively.

### Results:

A total of 471 and 442 HIV-controllers were included from the SHCS and ICSC, respectively. Among them, 115 (24.2%) and 233 (52.7%) were LTNP-Cs, respectively. No SNP or gene association with the LTNP-C phenotype in the individual GWAS or in the meta-analysis after multiple testing corrections was found (Table 1). However, those SNPs previously associated with natural HIV control linked to HLA-B (rs2395029 [p=0.0004; OR=1.82], rs9266409 [p=0.003; OR=1.42], rs59440261 [p=0.00004; OR=1.97]), MICA (rs11224303 [p=0.0005; OR=1.54]) and PSORS1C1 loci (rs3815087 [p=0.026; OR=1.28]) showed nominal association with this phenotype.

### Conclusion:

Genetic factors associated with the long-term HIV-controllers without risk of immunologic progression are those previously related to the overall HIV-controller phenotype. The results could help us to understand the biological

factors underlying this persistent non-progressor HIV controller phenotype as a crucial issue to consider these subjects as a good model of functional cure and, therefore, for the design of strategies for preventing HIV progression and personalized treatment strategies to those subjects who show CD4+ T cell loss.

**Table 1.** Best single locus results (p<10<sup>-4</sup>) using the meta-analysis tool in plink.

| CHR | Gene   | SNP        | BP        | A1 | p        | p(R)     | OR     | OR(R)  | Q      | I | SHCS           |                  | ICSC           |                  |
|-----|--------|------------|-----------|----|----------|----------|--------|--------|--------|---|----------------|------------------|----------------|------------------|
|     |        |            |           |    |          |          |        |        |        |   | p <sub>i</sub> | OR (95%CI)       | p <sub>i</sub> | OR (95%CI)       |
| 7   | CADPS2 | rs17144504 | 122152765 | C  | 1.84E-06 | 1.84E-06 | 0.5591 | 0.5591 | 0.5169 | 0 | 0.0003         | 1.62 (1.19-2.20) | 0.0004         | 1.68 (1.25-2.25) |
| 12  | N      | rs2730538  | 74073130  | T  | 3.30E-06 | 3.30E-06 | 1.6535 | 1.6535 | 0.8624 | 0 | 0.002          | 1.62 (1.19-2.20) | 0.0004         | 1.68 (1.25-2.25) |
| 1   | CYP4ZP | rs5003006  | 47351034  | T  | 6.37E-06 | 6.37E-06 | 0.5815 | 0.5815 | 0.3393 | 0 | 0.021          | 0.66 (0.46-0.94) | 6.2E-05        | 0.52 (0.38-0.71) |
| 7   | CADPS2 | rs7795913  | 12210503  | C  | 7.06E-06 | 7.06E-06 | 0.5818 | 0.5818 | 0.7852 | 0 | 0.001          | 0.56 (0.39-0.80) | 0.001          | 0.59 (0.43-0.80) |
| 11  | CDOM4* | rs557831   | 125813286 | A  | 7.47E-06 | 7.47E-06 | 0.6015 | 0.6015 | 0.6387 | 0 | 0.001          | 0.56 (0.39-0.80) | 0.001          | 0.62 (0.47-0.83) |

CHR, Chromosome; SNP, Single Nucleotide Polymorphism; BP, Base pair position according to UCSC genome browser (NCBI07/hg19) and dbSNP build 142; A1, Reference allele (minor allele); p, Fixed-effects p-value; p(R), Random-effects p-value; OR, Fixed-effects Odds Ratio (for being LTNP-C); OR(R), Random-effects OR; Q, p-value for heterogeneity of OR; I, effect size for heterogeneity of OR; SHCS, Swiss HIV Cohort Study; ICSC, International HIV-controllers Study Cohort; CI, Confidence interval.

\* Closer gene within 200 kilobases.

## 225 lncRNA REGULATES METABOLISM IN MYELOID DENDRITIC CELLS FROM HIV-1 ELITE CONTROLLERS

**Ciputra A. Hartana**<sup>1</sup>, Yelizaveta Rassadkina<sup>1</sup>, Ce Gao<sup>1</sup>, Enrique Martin-Gayo<sup>2</sup>, Bruce D. Walker<sup>1</sup>, Mathias Lichterfeld<sup>1</sup>, Xu G. Yu<sup>1</sup>

<sup>1</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>2</sup>Universidad Autónoma de Madrid, Madrid, Spain

**Background:** An HIV-1-specific T cell response is commonly regarded as the backbone of antiviral immunity in persons with natural control, while the specific contribution of innate immune cells to such a remarkable disease outcome is less clear. Myeloid dendritic cells (mDCs) are of particular interest, as they play key roles in priming of antiviral T cell responses and have the ability to persist long-term in functionally enhanced modification states in ECs.

**Methods:** Primary mDCs from HIV-1 elite controllers (ECs; n=23) were compared to highly active antiretroviral treated HIV-1-infected patients (HAARTs; n = 13) and HIV-1 negative healthy donors (HIVNs; n = 61), using RNAseq and CUT&RUN assays to assess the expression of long noncoding RNAs (lncRNAs) and histone modifications, respectively. Seahorse assays were used to analyze metabolic activities of mDCs. lncRNA expression in mDCs was evaluated by PrimeFlow RNA FACS.

**Results:** lncRNA MIR4435-2HG was upregulated in primary mDCs from ECs compared to HIVNs (P = 5.5e-06) and HAARTs (P = 5.8e-05). Expression of MIR4435-2HG was highly correlated to differentially expressed genes in ECs (n=924) that were enriched in Oxidative Phosphorylation and mtOR/EIF2 metabolic pathways. Upregulation of MIR4435-2HG in ECs was associated with increased oxidative phosphorylation and glycolysis activities, as shown by elevated oxygen consumption rates and extracellular acidification rates in response to TLR3 stimulation using Poly(I:C) in mDCs. Silencing of MIR4435-2HG by siRNA reduced the metabolic states of mDCs. Using the PrimeFlow RNA detection assay, we observed that MIR4435-2HG was expressed in a mDC cell cluster endowed with increase abilities for antigen presentation and previously described as "DC4", accounting for more than 60% of all mDCs in ECs and <25% in HIVNs (P = 0.0006). Notably, using CUT&RUN assay, we observed significantly increased H3K27ac enrichment at an intronic enhancer region within the RPTOR gene, the main component of mTORC1, in mDCs from ECs compared to HIVNs (P = 0.0286). This genomic locus was specifically predicted to be susceptible to triple-helix formation between chromosomal double-stranded DNA and MIR4435-2HG by the Triplex Domain Finder (TDF) algorithm.

**Conclusion:** These results suggest a previously unrecognized role of MIR4435-2HG for enhancing the immunometabolic activities of mDCs in ECs through targeted epigenetic modifications of RPTOR, a member of the mTOR signaling pathway.

## 226 DEFECTIVE FUNCTIONS OF HIV ENVELOPE GLYCOPROTEIN ASSOCIATE WITH LONG-TERM HIV CONTROL

**Silvia Pérez Yanes**<sup>1</sup>, Concepción Casado<sup>2</sup>, María Pemas<sup>2</sup>, Romina Cabrera-Rodríguez<sup>1</sup>, Judith Estévez-Herrera<sup>1</sup>, Daniel Márquez-Arce<sup>1</sup>, Isabel Olivares<sup>2</sup>, Víctor Urrea<sup>3</sup>, Silvia Marfil<sup>3</sup>, Raquel Ortiz<sup>2</sup>, Carla Roviro<sup>3</sup>, Cecilio López-Galíndez<sup>2</sup>, Agustín Valenzuela-Fernández<sup>1</sup>, Julià Blanco<sup>3</sup>, for Romina Cabrera

<sup>1</sup>Universidad de La Laguna, San Cristóbal de La Laguna, Spain, <sup>2</sup>Instituto de Salud Carlos III, Madrid, Spain, <sup>3</sup>Institut de Recerca de la SIDA, Badalona, Spain

**Background:** The viral envelope glycoprotein complex (Env) is essential in the first stage of HIV infection life cycle and its function has been associated to HIV pathogenesis. Therefore, we explored the relationship between the Env functions and the long-term viral load control in HIV-infected individuals.

**Methods:** We genotypically and phenotypically characterized 41 Envs from 29 patients with different clinical progression rates. 10 Envs isolated from 7 Long Term Non Progressors-Elite Controllers (LTNP-EC) individuals with undetectable VL for >20 years and infected in the 90's; 10 Env clones isolated from 6 viremic LTNPs with detectable VL<10,000/copies/mL also infected in the 90's. As reference, we analyzed 10 Envs obtained from 6 HIV-1 individuals infected in the 90's, but with high VL>10<sup>5</sup> and a normal chronic infection (Ancient-P) and 11 viral clones from 10 HIV-1 individuals infected between 2013-2014 and with similar VL (Modern-P). We analyzed cell-surface expression levels by flow cytometry; fusogenicity in cell-to-cell fusion assays; CD4 affinity in a viral transfer capacity, which exclusively depends on the binding of gp120 to the CD4 receptor; and infectivity of cell-free viruses in TZM-bl cells.

**Results:** We did not observe statistically significant differences in cell-surface expression among the four different Env groups. However, a statistically significant lower fusogenicity, CD4 binding and infectivity was observed in Env isolated from LTNP compared to Ancient-P and Modern-P (p<0.05 in all cases). NO differences in these parameters were observed between EC and viremic LTNPs. Genotypic analysis showed differences in the length and glycosylation sites of Env, mainly impacting the V5 loop that showed shorter length in both groups pf LTNPs. Lower differences were observed in V1-V2 and V4 loops, while V3 loop remained constant among groups. In general, we observed that shorter and less glycosylated Env had lower expression, fusion and transfer capacity.

**Conclusion:** Our data suggest that there is a link between critical Env-associated viral functions and the clinical progression of the studied individuals. Our data support the hypothesis that poorly functional viral Envs could be critical for the control of viral replication and HIV pathogenesis. These viral characteristics represent potential new anti-HIV biomarkers for the development of innovative therapeutic strategies.

## 227 ELEVATED PLASMA CYTOKINES IN ELITE CONTROL: IP-10 AND MIG PREDICT LOSS OF CONTROL

**Eva Poveda**<sup>1</sup>, Wendy Fitzgerald<sup>2</sup>, Cristina Reglero<sup>1</sup>, Manuel Crespo<sup>1</sup>, Ana Mariño<sup>3</sup>, Hortensia Álvarez<sup>2</sup>, Nieves Valcarce<sup>3</sup>, Anna Rull<sup>4</sup>, Ezequiel Ruiz-Mateos<sup>5</sup>, Leonid Margolis<sup>2</sup>, Michael M. Lederman<sup>6</sup>, Michael L. Freeman<sup>6</sup>, for the ECRIS Integrated in the Spanish AIDS Research Network

<sup>1</sup>Galicía Sur Health Research Institute, Vigo, Spain, <sup>2</sup>National Institute of Child Health and Human Development, Bethesda, MD, USA, <sup>3</sup>Hospital Arquitecto Marcide, Ferrol, Spain, <sup>4</sup>Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain, <sup>5</sup>Institute of Biomedicine of Seville, Sevilla, Spain, <sup>6</sup>Case Western Reserve University, Cleveland, OH, USA

**Background:** Elite controllers (EC) with a durable control of HIV-1 replication (persistent controllers) may represent a model of functional cure. We evaluated the cytokine profile in plasma 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 studied a median of 1.4 years before the loss of control, and 15 persistent controllers-PC) and 30 HIV-uninfected controls. Levels of 39 pro-inflammatory markers were quantified in plasma 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 cytokines were 2.2-fold higher for PLWH than for the control group. Within PLWH, EC showed the highest levels (2.3- and

2.5-fold higher than for ART-exposed and ART-naïve, respectively), and within the EC group, levels were 1.7-fold higher for TC compared to PC. Higher levels of MIG and IL-8 best distinguished PLWH from uninfected controls (AUC 0.841 and 0.783, respectively). Specifically, MIG discriminates with a sensitivity of 77% and a specificity of 83%. In the context of suppressed viremia (EC and ART-exposed), higher levels of IL-18 and TNF were associated with EC (AUC of 0.911 and 0.967, respectively). IL-18 discriminates between EC and ART-exposed with a sensitivity of 80% and a specificity of 100%. Indeed, 83% of participants with IL-18 levels ≥ 20 pg/mL were correctly classified as EC. Finally, within EC, higher levels of MIG and IP-10 best distinguished TC and PC (AUC 0.711 and 0.760, respectively). IP-10 distinguished TC from PC with a sensitivity of 93% and a specificity of 53%. 89% of EC with IP-10 levels < 2082 pg/mL were correctly identified as PC.

**Conclusion:** EC showed higher plasma pro-inflammatory profile compared with other PLWH groups, levels were higher for EC who later lost control (TC) than for PC. Within the EC group, PC had lower levels of MIG and IP-10 than did TC, highlighting these cytokines as potential biomarkers that predict loss or sustained virologic control in the absence of treatment.

## 228 miRNA SIGNATURES IN CD4 T CELLS FROM PATIENTS WITH NATURAL CONTROL OF HIV INFECTION

**Ruben A. Ayala-Suarez**<sup>1</sup>, Francisco Díez-Fuertes<sup>1</sup>, Mercedes Bermejo<sup>1</sup>, Esther Calonge<sup>1</sup>, Lorna Leal<sup>2</sup>, Manel E. Bargalló<sup>2</sup>, Maria Jose Maleno<sup>2</sup>, Felipe Garcia<sup>2</sup>, Montserrat Plana<sup>2</sup>, José Alcamí<sup>3</sup>, for the ECRIS Integrated in the Spanish AIDS Research Network

<sup>1</sup>Institute of Health Carlos III, Madrid, Spain, <sup>2</sup>Hospital Clinic of Barcelona, Barcelona, Spain, <sup>3</sup>Institute de Salut Carlos III, Majadahonda, Spain

**Background:** Natural control of viral replication in the absence of antiretroviral therapy (ART) occurs in a small fraction of HIV+ individuals. Elite controllers (EC) efficiently control blood viral load under 50 cp/ml while viremic controllers (VC) maintain viral load under 2,000 copies/ml without ART. Distinct miRNA expression has been associated with cell populations in these patients. Hence, we explored the miRNome of CD4 T cells to identify a miRNA signature related to HIV infection control.

**Methods:** We performed miRNA-Seq in forty-four samples of CD4 T cells from EC (n=10), VC (n=10), HIV-negative individuals (HIV-; n=4), and typical progressors (TP) before (NT-TP; n=10) and after ART administration (ART-TP; n=10). Viral load was monitored for at least more than one year. Reads were aligned to miRBase v21 with Chimera and miRDeep2 and differential expression analysis was carried out between groups (FDR-adjusted q-value<0.1). Target genes were predicted using miRNet and filtered with NCBI's HIV-host protein interactome, checking for experimentally validated miRNA-gene interactions in DIANA-Tarbase 8.0 and miRTarBase v8.

**Results:** We found four downregulated miRNA in EC/VC vs TP (Fig.1): miR-1271-5p (log2 fold change (LFC)=-1.318), miR-501-3p (LFC=-1.043), miR-99b-5p (LFC=-0.855), and miR-125a-5p (LFC=-0.665), that likely regulate 822 host genes. Pathways potentially affected by the downregulation of these miRNA include ErbB and p53 signaling routes (q<5x10<sup>-4</sup>). Within these routes, miR-125a targets ErbB2, and TP53, and miR-99b targets CDKN1A. In addition, EC presents an upregulation of let-7c-5p vs NT-TP (FC=0.861; q<0.1), vs ART-TP (LFC=0.921; p<0.05), and vs TP (LFC=0.606; p<0.05), including TNPO3 and IL-10 as experimentally validated targets of this miRNA. Moreover, miR-221-5p, miR-192-5p, miR-484, miR-501-3p, and let-7f-5p (q<0.1) were downregulated in EC vs NT-TP and HIV- vs NT-TP comparisons.

**Conclusion:** We observe a specific signature of four downregulated miRNA in ECs' and VCs' CD4 T cells compared to TPs. These miRNAs regulating the expression of ErbB2, p53, and CDKN1A may produce the activation of the p53 signaling route, fostering cell cycle arrest and a pro-apoptotic state, as well as the CDKN1A-mediated HIV restriction. The upregulation of let-7c-5p reveals a specific mechanism in ECs, which may modulate pre-integration complex nuclear transport and site-directed integration through TNPO3. Besides, similar miRNA signatures have been found in ECs and HIV-.

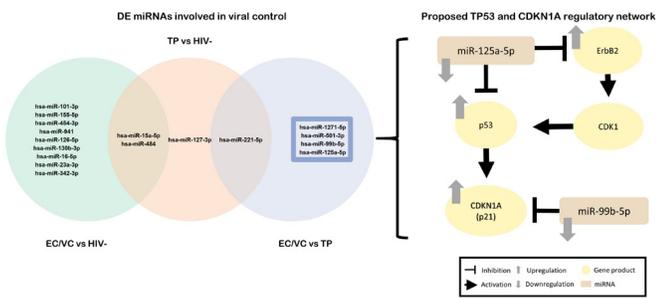


Figure 1. Left panel: Differentially expressed miRNA between natural controllers (EC and VC), typical progressors and HIV-negative patients. Right panel: Regulation network of miRNA in p53 signaling pathway in HIV controllers.

**229 THE VON HIPPEL–LINDAU CULLIN-RING E3 LIGASE REGULATES APOBEC3 CYTIDINE DEAMINASES**

Gael Scholtes<sup>1</sup>, Aubrey Sawyer<sup>1</sup>, Isabelle Clerc<sup>1</sup>, Meejeon Roh<sup>1</sup>, Chisu Song<sup>1</sup>, Richard T. D'Aquila<sup>1</sup>

<sup>1</sup>Northwestern University, Chicago, IL, USA

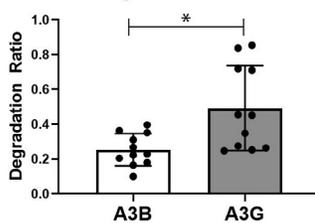
**Background:** Human apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3; A3) cytidine deaminases can either promote cancer progression or defend against HIV. Nuclear-localized A3s, such as A3B, are at low or non-existent levels in primary cells, and often up-regulated in cancer cells causing pathogenic chromosomal mutagenesis. In contrast, increasing T lymphocyte content of cytoplasmic A3G decreases infectivity of progeny VIF-positive HIV virions in vitro. It is not known how A3s are regulated in uninfected cells. Here, we studied the regulation of A3 proteins in uninfected cells.

**Methods:** Cancer cell lines with endogenous A3 expression and 293T cells expressing HA-tagged A3s were studied. We performed mass spectrometry to identify candidate A3-interacting proteins. Effects of a candidate interactor, the von Hippel–Lindau tumor suppressor (pVHL), on cellular A3 levels, as detected by immunoblotting, were characterized by genetic knockdown, over-expression, and co-immunoprecipitation.

**Results:** Levels of an endogenous A3 were reproducibly increased by epoxomicin, an irreversible proteasome inhibitor. An A3 interaction with pVHL was identified by a proteomic analysis. siRNA knockdown of pVHL increased levels of an endogenous A3. Ectopic expression of pVHL decreased levels of each A3 (A3A, B, C, D, F, G, H and HII). This decrease was dependent on CRLpVHL formation, as it was not seen with co-transfection of C162F mutant pVHL which lacks Elongin C binding capacity. The E3 ligase ARIH1 potentiated pVHL-mediated degradation of each A3, except A3H. Finally, CRLpVHL more effectively degraded nuclear, pro-cancer A3B than the cytoplasmic, anti-retroviral A3G (Figure shows ratio of A3 immunoblot band intensity normalized to Lamin in 11 lysates of 293Ts co-transfected with Flag-pVHL and either HA-A3B or -A3G, divided by normalized control HA-A3 intensity in absence of pVHL. P = 0.03, Wilcoxon).

**Conclusion:** A cellular mechanism of A3 regulation requires formation of CRLpVHL. pVHL serves as a substrate receptor in that complex, facilitating ubiquitination and proteasomal degradation of target proteins. This parallels the well-characterized mechanism of retroviral VIF in A3 degradation. The observation of better pVHL-mediated degradation of A3B than A3G suggests the possibility of decreasing A3B-accelerated cancer progression without impairing the A3G anti-HIV intrinsic immune defense in people living with HIV (PLWH).

**A3B is more susceptible to pVHL-mediated degradation than A3G**



**230 RESTRICTION OF HIV-1 INFECTION IN SICKLE CELL TRAIT**

Sergei Nekhai<sup>1</sup>, Namita Kumari<sup>1</sup>, Mehdi Nouraie<sup>2</sup>, Javed Khan<sup>1</sup>, Sharmin Diaz<sup>1</sup>, Asrar Ahmad<sup>1</sup>, Patricia E. Houston<sup>1</sup>, Songping Wang<sup>1</sup>, Miguel D. Rougier<sup>3</sup>, Douglas Nixon<sup>3</sup>, Sohail Rana<sup>1</sup>, James G. Taylor<sup>1</sup>, M. Neale Weitzmann<sup>4</sup>, Seble Kassaye<sup>5</sup>, for the WIHS Group

<sup>1</sup>Howard University, Washington, DC, USA, <sup>2</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>3</sup>Weill Cornell Medicine, New York, NY, USA, <sup>4</sup>Emory University, Atlanta, GA, USA, <sup>5</sup>Georgetown University, Washington, DC, USA

**Background:** Patients with Sickle cell disease (SCD), an inherited hemoglobinopathy that affects approximately 100,000 people in the U.S, have lower risk for HIV-1 infection. We previously showed that ex vivo HIV-1 infection is restricted in SCD peripheral blood mononuclear cells (PBMCs), in part, due to the upregulation of antiviral, inflammatory and hemolytic factors including heme oxygenase-1 (HO-1) that has demonstrated direct antiviral effect against HIV-1. As individuals with sickle cell trait (SCT) may develop mild hemolysis, we investigated whether SCT PBMCs restrict HIV-1 infection ex vivo mediated by the intrinsic antiviral factors including HO-1, and whether people living with HIV (PLWH) with SCT exhibit higher levels of CD4.

**Methods:** Ex vivo HIV-1 infection was analyzed SCT PBMCs obtained using IRB approved protocols. We used a custom designed array of 42 known restriction factors to analyze their expression in SCT PBMCs. Women's Interagency HIV Study (WIHS) samples were obtained from WIHS repositories and genotyped for SCT trait. The population level effect of SCT on HIV-1 prevalence was analyzed using mixed effect linear model (using random intercept) models.

**Results:** SCT PBMCs infected with HIV-1 ex vivo showed ~2-fold reduction of HIV-1 replication and lower levels of HIV-1 reverse transcription products, 2-LTR circles, integration and gag RNA expression. SCT PBMCs had higher HO-1 mRNA and protein levels and reduced RNR2 protein levels. HO-1 inhibition by tin porphyrin eliminated HIV-1 restriction in this ex vivo model. To determine the potential clinical significance of these findings, we studied Howard University clinic recruits and found higher levels of HO-1 and RNR2 mRNA and lower HIV-1 p24 levels among PLWH individuals with SCT. To determine the population level effect of SCT on HIV-1 prevalence, we assessed SCT trait among women living with HIV (WLH) in the Women Interagency HIV-1 Study (WIHS). Among African American participants in the WIHS, prevalence of SCT was lower among women with HIV compared with uninfected women 8.7% vs 14.2%, (OR 0.57, 95%CI = 0.36–0.92, p=0.020). WIHS WLC with SCT had higher levels of CD4+/CD8+ ratios over 20 years of follow up (p=0.003) than matched WLH without SCT (Table 1).

**Conclusion:** Our findings suggest that HIV-1 restriction factors including HO-1 and RNR2 might restrict HIV-1 infection among individuals with SCT and limit the pathogenicity of HIV.

Table 1. Prevalence of HIV-1 infection in WIHS cohort of African American women with sickle cell trait.

| Genotype     | HIV-1        |              | Total       |
|--------------|--------------|--------------|-------------|
|              | Negative (%) | Positive (%) |             |
| AA           | 224 (82.8%)  | 441 (91.3%)  | 665 (89.4%) |
| AS           | 37 (14.2%)   | 42 (8.7%)    | 79 (10.6%)  |
| <b>Total</b> | <b>261</b>   | <b>483</b>   | <b>744</b>  |

**231 IFNL4 RS368234815 SNP IS ASSOCIATED WITH CD4:CD8 RATIO NORMALISATION IN PWH ON ART**

Serkan Aydemir Aydemir<sup>1</sup>, Christine Kelly<sup>1</sup>, Marija Leoncikaite<sup>1</sup>, Pdraig McGettrick<sup>1</sup>, Aoife G. Cotter<sup>1</sup>, Gerard Sheehan<sup>1</sup>, John S. Lambert<sup>1</sup>, Eavan G. Muldoon<sup>1</sup>, Eoin Feeney<sup>1</sup>, Patrick Mallon<sup>1</sup>, Willard Tinago<sup>1</sup>, for the All Ireland Infectious Diseases (AIID) Cohort Study

<sup>1</sup>University College Dublin, Dublin, Ireland

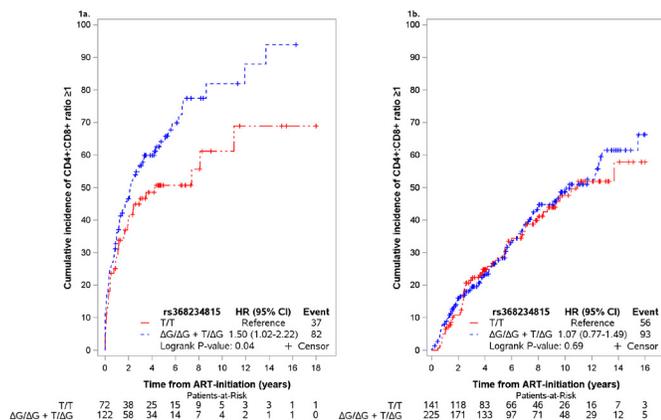
**Background:** The interferon lambda (IFNL) single nucleotide polymorphism (SNP) rs368234815 has been associated with altered host responses to viral infection. We aimed to determine its impact on CD4:CD8 T-cell ratio normalisation in people with HIV (PWH)

**Methods:** We analysed T-cell responses in PWH enrolled in the All Ireland Infectious Diseases (AIID) cohort who initiated ART starting January 2001 and had more than one T-cell subset measured at least 6 months later. IFNL4 genotyping was performed on genomic DNA employing allelic discrimination. We collated demographic (age, sex, ethnicity, HIV acquisition risk), clinical and treatment (ART regimens, CD4 and CD8 T-cell counts, HIV RNA) data.

Primary outcome was time to normalisation of CD4:CD8 ratio ( $\geq 1$ ). We used Cox regression models to evaluate associations between ratio normalisation and IFNL4 rs368234815 alleles ( $\Delta G/\Delta G$  or  $T/\Delta G$  and  $T/T$ ). Data are median [IQR] unless specified.

**Results:** 560 PWH, age 34.7 (29.5–40.7) years, 61% male, 53% Caucasian, 48% heterosexual transmission, followed for 7.4 (4.3–11.7) years after ART initiation were included. Nadir CD4 count was 267 (151–414.5) cells/mm<sup>3</sup>, 39% and 36% were initiated on an NNRTI or PI. Overall 268 (47.8%) achieved a CD4:CD8 ratio  $\geq 1$ , with median 7.6 (95% CI 6.6–9.4) years to ratio normalisation. The probability of CD4:CD8  $\geq 1$  was estimated at 16 (13.0–19.1)%, 32 (27.5–35.5)%, 38.8 (34.3–42.9)% and 56.5 (51.0–61.3)% at years 1, 3, 5 and 10 respectively. Those with a baseline CD4  $\geq 350$  cells/mm<sup>3</sup> were significantly more likely to achieve CD4:CD8  $\geq 1$  (HR=2.73 (2.13, 3.49)  $p < 0.001$ ). PWH with baseline CD4 T-cell count  $\geq 350$  and expressing IFNL4 rs368234815 ( $\Delta G/\Delta G$  or  $T/\Delta G$ ) were more likely to achieve CD4:CD8  $\geq 1$  compared to those with  $T/T$  major homozygosity (HR=1.51, 95% CI (1.02, 2.23),  $P=0.038$ , Figure 1a). There was no association between rs368234815 and CD4:CD8 normalisation in subjects with baseline CD4+ <350 cells/mm<sup>3</sup> (Figure 1b). The association between rs368234815 ( $\Delta G/\Delta G$  or  $T/\Delta G$ ) and CD4:CD8 normalisation persisted in analyses adjusted for gender, ethnicity, HIV transmission risk and age fitted as either a continuous (HR=1.59 (1.06, 2.38),  $P=0.024$ ) or fractional polynomial (HR=1.49 (1.00, 2.23),  $P=0.049$ ) variable.

**Conclusion:** In PWH starting ART with a CD4 count  $\geq 350$ , rs368234815 IFNL4 ( $\Delta G/\Delta G$  or  $T/\Delta G$ ) is associated with an increased likelihood of CD4:CD8 ratio normalisation. The role of IFNL4 in modulating persistent inflammation on ART warrants further investigation



## 232 REPLICATED EPIGENETIC ASSOCIATIONS WITH SCD14 AMONG MEN WITH HIV INFECTION

**Boghuma K. Titanji<sup>1</sup>**, Zeyuan Wang<sup>1</sup>, Qin Hui<sup>1</sup>, Kaku So-Armah<sup>2</sup>, Matthew Freiberg<sup>3</sup>, Amy Justice<sup>4</sup>, Ke Xu<sup>4</sup>, Vincent Marconi<sup>1</sup>, Yan Sun<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Boston University, Boston, MA, USA, <sup>3</sup>Vanderbilt University, Nashville, TN, USA, <sup>4</sup>Yale University, New Haven, CT, USA

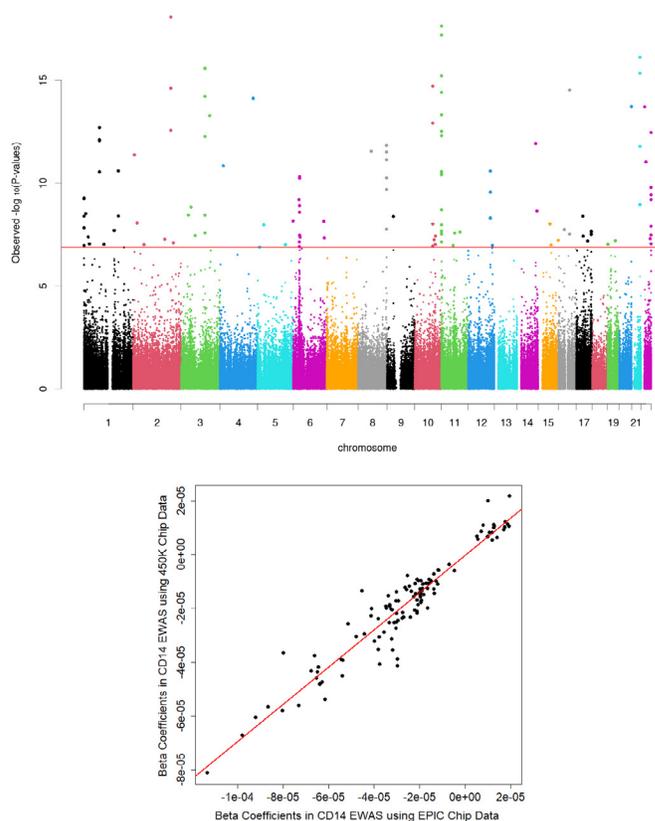
**Background:** HIV-infection is characterized by chronic inflammation and immune activation. sCD14 is an important marker for monocyte activation due to microbial translocation and the pathogenesis of HIV. Elevated plasma levels of sCD14 predicts all-cause mortality in people with HIV (PWH). Epigenetic processes, can offer clues into the pathophysiology of inflammatory processes and provide insight for new therapeutic approaches. To date, epigenetic associations with circulating sCD14 levels among PWH are unknown. In this study, we conducted an EWAS of sCD14 levels among PWH and performed replication and meta-analyses to identify epigenetic markers, genes, and pathways linked to sCD14 via DNA methylation changes.

**Methods:** We conducted an EWAS of sCD14 among 1,074 HIV-positive male participants in the Veterans Aging Cohort Study (VACS) to identify epigenetic signatures of sCD14. Samples were processed at the time of collection. The epigenome-wide DNA methylation levels were measured using the Illumina Infinium Methylation 450K (n=549) and EPIC (850K) BeadChip (n=525). We adjusted for age, race, CD4 count, viral load, body mass index (BMI), hepatitis B and C infection, smoking status, alcohol use and cell type proportions in peripheral blood within each chip type, and conducted meta-analysis to identify

**Results:** The mean age of participants was 52.7 years. 84.5% were African American, 10.4% Caucasian, 2.7% Hispanic and 2.4% classified as Other. The

average BMI was 25.6 kg/m<sup>2</sup>, and around 79.8% of participants had a smoking history. By surveying more than 300,000 cytosine guanine dinucleotide (CpG) measured from both chips, we identified 118 sites significantly associated with sCD14 (Bonferroni corrected  $p$ -value  $< 0.05$ ) in the meta-analysis. The majority of these sCD14-association CpG sites (98 sites, 83%) were negatively associated with sCD14 levels. All sites had consistent associations between 450K and EPIC chip data (all in the same direction, Pearson correlation  $R^2$  of 0.91). CpG site of cg00676801 (STAT1) has the most significant association with sCD14 ( $p$ -value of  $8.43 \times 10^{-19}$ ).

**Conclusion:** We uncovered novel epigenetic associations with sCD14 in PWH. This was a first step in investigating the relationship between HIV, DNA methylation and inflammatory markers. Further studies are warranted to examine the role of these epigenetic changes in the mechanisms of chronic inflammation and its implications for chronic disease and mortality in PWH.



## 233 TH17 CELL MASTER TRANSCRIPTION FACTOR RORC2 REGULATES HIV GENE EXPRESSION AND LATENCY

**Tomas Raul Wiche Salinas<sup>1</sup>**, Yuwei Zhang<sup>1</sup>, Daniele Sarnello<sup>2</sup>, Alexander Zhyvoloup<sup>2</sup>, Laurence Raymond Marchand<sup>1</sup>, Delphine Planas<sup>1</sup>, Manivel Lodha<sup>2</sup>, Debashree Chatterjee<sup>1</sup>, Katarzyna Karwacz<sup>2</sup>, Sally Oxenford<sup>2</sup>, Jean-Pierre Routy<sup>3</sup>, Heather Amrine-Madsen<sup>4</sup>, Petronela Ancuta<sup>1</sup>, Ariberto Fassati<sup>2</sup>

<sup>1</sup>Centre de Recherche du CHUM, Montreal, Canada, <sup>2</sup>University College London, London, UK, <sup>3</sup>McGill University Health Centre, Montreal, Canada, <sup>4</sup>ViiV Healthcare, Research Triangle Park, NC, USA

**Background:** Among CD4+ T-cells, T helper 17 (Th17) cells ensure defenses against bacterial/fungal pathogens at mucosal barriers. During HIV-1 infection, Th17 cells are highly susceptible to infection and depleted from mucosal sites, resulting in mucosal barrier integrity alterations, microbial translocation, systemic inflammation, and disease progression. Additionally, HIV-infected Th17 cells can be long-lived and harbor viral reservoirs (VR) in people living with HIV (PLWH) receiving antiretroviral therapy (ART). Thus, Th17 cells are key players in HIV pathogenesis and VR persistence. Here, we evaluated the role of RORC2, the master regulator of Th17 cell differentiation, on HIV replication and latency.

**Methods:** Memory CD4+ T-cells were isolated from PBMCs of HIV-uninfected individuals (HIV-), ART-treated (ART+PLWH) and untreated (ART-PLWH) PLWH by negative selection using magnetic beads. Subsequently, cells expressing

the Th17 markers RORC2 and CCR6 were isolated by FACS. The NL4.3BAL and transmitted/founder THRO HIV-1 strains were used for infections in vitro. A viral outgrowth assay (VOA) was performed with cells from ART+PLWH and ART-PLWH. HIV replication/outgrowth were evaluated by FACS and ELISA. HIV integration was evaluated by nested real-time PCR. RORC2 silencing via shRNA transduction in Jurkat cells and siRNAs nucleofection in primary T-cells was performed. RORC2 overexpression was performed in 293T and Jurkat cells infected with VSV-G-pseudotyped HIV-1 LAI env-GFP (HIV-1GFP). For Chromatin immune precipitation (ChIP) experiments, Jurkat cells transduced with a retroviral vector expressing RORC2-myc were infected with HIV-1GFP. Real time PCR signal for HIV LTR NRRE-1 and HIV CS Pol was subsequently evaluated.

**Results:** The inhibition of RORC2 by tool small molecule decreased HIV replication in CD4+ T-cells in vitro, as well as viral outgrowth from T cells of ART+PLWH and ART-PLWH. Consistently, RORC2 expression was higher within HIV-p24+ compared to total T-cells in ART-PLWH upon TCR triggering in vitro. Moreover, CCR6+RORC2+ compared to CCR6-RORC2- T cells of ART+PLWH were enriched in proviral DNA ex vivo. Furthermore, RORC2 silencing inhibited HIV-1 infection, specifically in CCR6+ T cells, whereas RORC2 overexpression led to enhanced viral replication in cell lines and primary cells. Finally, RORC2 promoted viral gene expression and ChIP revealed that RORC2 binds to the HIV-1 promoter.

**Conclusion:** Altogether, these results point to RORC2 as a new Th17-specific target for HIV-1 therapy.

### 234 miR-422a: A TYPE I INTERFERON-REGULATED MODULATOR OF HIV REPLICATION

Li Du<sup>1</sup>, Mohamed Bouzidi<sup>1</sup>, Hannah Sperber<sup>1</sup>, Samuel D. Abrams<sup>2</sup>, Karla Medina<sup>1</sup>, Zain Y. Dossani<sup>1</sup>, Satish Pillai<sup>3</sup>

<sup>1</sup>Vitalant Research Institute, San Francisco, CA, USA, <sup>2</sup>Colorado State University, Fort Collins, CO, USA, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** The cytokine interferon- $\alpha$  (IFN $\alpha$ ) potently suppresses HIV replication and may accelerate clearance of the latent HIV reservoir. The mechanisms underlying this anti-HIV activity remain to be elucidated. We previously reported that the microRNA (miRNA) miR-422a was the sole miRNA downregulated by IFN- $\alpha$  treatment in HIV-infected individuals in vivo, and the extent of miR-422a reduction significantly correlated with viral load reduction. Here, we investigated the molecular basis of this relationship by examining miR-422a effects on HIV replication, latency, and the antiviral capacity of IFN- $\alpha$  ex vivo.

**Methods:** PBMCs were obtained from HIV-uninfected individuals, and CD4+ T cells were isolated using negative selection. RT-PCR was used to measure miR-422a expression in untreated and anti-CD3/28-stimulated CD4+ T cells with or without 1000 units of IFN $\alpha$ . miR-422a-overexpressing and knockout stable Jurkat cell lines were constructed using lentiviral transduction. miR-422a mimic and antagomir were synthesized and transfected into Jurkat cells and primary CD4+ T cells using HiPerfect. Transduced or transfected cells were infected with HIV NL4-3, and HIV replication was measured by p24 ELISA and flow cytometry (Gag). Total RNA-seq was used to evaluate effects of miR-422a overexpression and knockdown on the primary CD4+ T cell transcriptome (N=3 donors). Paired t tests were used to analyze data and FDR was calculated to account for multiple comparisons.

**Results:** IFN $\alpha$  decreased HIV Gag ( $p=0.023$ ) and p24 expression ( $p=0.0028$ ). IFN $\alpha$  downregulated miR-422a in Jurkat ( $p=0.029$ ) and in primary CD4+ T cells ( $p=0.001$ ), while HIV infection ( $p=0.006$ ) or anti-CD3/28 stimulation ( $p=0.0055$ ) upregulated miR-422a in primary cells ( $p=0.006$ ). miR-422a overexpression increased HIV replication ( $p=0.014$ ), and miR-422a knockdown inhibited HIV replication ( $p=0.00023$ ) in primary cells. IFN $\alpha$ -induced HIV suppression was counteracted by miR-422a mimic ( $p=0.0089$ ) and enhanced by miR-422a antagomir ( $p=0.0061$ ) in primary cells. RNA-seq data revealed that chromatin and chromosome organization were significantly modulated by miR-422a manipulation (FDR = 0.004).

**Conclusion:** miR-422a is a key host factor induced by HIV infection and TCR stimulation which supports HIV replication and persistence in the CD4+ T cell compartment via epigenetic effects. Suppression of miR-422a is a critical step underlying IFN $\alpha$  anti-HIV activity. Our data suggest that pharmacologic manipulation of miR-422a should be explored as an HIV cure strategy.

### 235 GUT OX40+CD4+ T CELLS STRONGLY CORRELATE WITH MARKERS OF PROGRESSION IN TREATED HIV

Isaac Rosado-Sánchez<sup>1</sup>, Inés Herrero-Fernández<sup>1</sup>, Salvador Sobrino<sup>1</sup>, Ana Eloisa Carvajal<sup>2</sup>, Miguel Genebat<sup>3</sup>, Laura Tarancon-Diez<sup>1</sup>, María Fontillón<sup>1</sup>, Rocio M. De Pablo<sup>2</sup>, Manuel Leal<sup>1</sup>, Yolanda M. Pacheco-López<sup>1</sup>

<sup>1</sup>Institute of Biomedicine of Sevilla, Sevilla, Spain, <sup>2</sup>University of Sevilla, Sevilla, Spain, <sup>3</sup>Hospital Universitario Virgen del Rocío, Sevilla, Spain

**Background:** OX40 (TNFRSF4, CD134) has a protector role in long-term cell viability of memory T cells, particularly during clonal proliferation. Besides, OX40+CD4+ T-cells are metabolically active cells expressing high levels of Glut1. Remarkably, in treated-subjects, circulating OX40+CD4+ T-cells were enriched for clonally expanded HIV-1 sequences and Glut1+OX40+CD4+ T-cells were shown permissive to in vitro HIV infection without external activating stimuli. Thus, OX40+CD4+ T-cells have been clearly related to HIV reservoir. However, such relevant T-cell subset has not been yet focused. We characterized this subset in gut mucosa, main site for HIV reservoir, and explored their potential relation with relevant markers of progression

**Methods:** Biopsies of caecum and terminal ileum of treated, virally-suppressed HIV-subjects (n=32) were obtained. By flow cytometry, OX40+CD4+ T-cells and Ki67+CD4+ T-cells, both representing proliferating subsets, were analyzed in MMCs and PBMCs. Several tissue T-cell subsets impacting mucosal integrity and homeostasis were also analyzed (Treg, Th17, Th22). Mucosal damage was estimated using a semi-quantitative scale by observation of histological sections. Soluble markers of inflammation (CRP, D-dimers,  $\beta$ 2M) and thymic output ( $\delta/\beta$  TREC ratio) were quantified in blood samples. Potential associations between mucosal OX40+CD4+ T-cells and the rest of parameters were explored using Spearman rank test

**Results:** Much higher frequencies of OX40+CD4+ T-cells were observed among mucosal, particularly at caecum, than circulating cells (Figure, panel A). Ki67+CD4+ subsets slightly correlated with those expressing OX40 and were less frequent in all locations. We explored associations between all these subsets and markers of HIV progression and the strongest were observed between caecum OX40+CD4+ T-cells and nadir CD4, CD4/CD8 ratio, neutrophil-to-lymphocyte ratio, thymic output and mucosal damage at caecum (Figure, panel B). A strong inverse correlation was also observed between caecum OX40+CD4+ T-cells and Th22 ( $r=-0.64$ ;  $p=0.001$ )

**Conclusion:** Mucosal OX40+CD4+ T-cells, particularly at caecum, show notable associations with mucosal damage as well as with relevant clinical, inflammatory and homeostasis-related parameters. Besides potentially representing a main cellular HIV reservoir (work in progress!), this cellular subset could be also involved in main homeostasis-related alterations subjacent in treated subjects

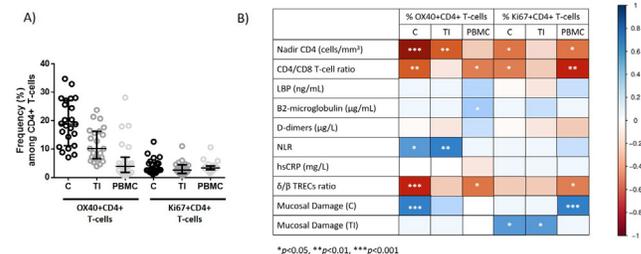


Figure. Frequencies of OX40+CD4+ and Ki67+CD4+ T-cells in gut mucosal and circulating cells (A). Correlations tested by Spearman rank test (B), color cells show the strength of association (rho), the positive ones in blue and the negatives ones in red, and the number of asterisks show statistical significance as indicated below the table. C, Caecum; TI, Terminal Ileum; PBMC, Peripheral Blood Mononuclear Cells; LBP, Lipopolisaccharide-binding protein; NLR, Neutrophil-to-Lymphocyte ratio; TRECs, T-cell Receptor Excision Circles.

### 236 INTERLEUKIN-7 IS A POTENT INDUCER OF ANTI-HIV-1 CHEMOKINES

Hana Schmeisser<sup>1</sup>, Samuel Owusu<sup>1</sup>, Olivia I. Hansen<sup>1</sup>, Qingbo Liu<sup>1</sup>, Yuna Seo<sup>1</sup>, Huiyi Miao<sup>1</sup>, Raffaello Cimbro<sup>2</sup>, Timothy G. Myers<sup>1</sup>, Claire Deleage<sup>3</sup>, Anthony S. Fauci<sup>1</sup>, Paolo Lusso<sup>1</sup>

<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>2</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA

**Background:** Interleukin-7 (IL-7) is a non-redundant cytokine that may play a key role in promoting T-cell reconstitution in HIV-1 infection. However, the effects of IL-7 on HIV-1 replication are still largely undefined. To investigate the role of IL-7 in HIV-1 infection, we tested the ability of recombinant human IL-7

to induce the production of anti-HIV-1 chemokines (CCL3/MIP-1 $\alpha$ , CCL4/MIP-1 $\beta$ , and CCL5/RANTES).

**Methods:** PBMC from healthy human blood donors were cultured in the presence or absence of IL-7 at supra-homeostatic concentrations (25 ng/mL) and 5-fold dilutions thereof in the absence of any other concomitant stimulation. Culture supernatants as well as cells pellets were collected at 24-, 48- and 72-hours post-treatment and tested for levels of secreted chemokines by ELISA or activation of signaling pathways by WB. The effect of antiviral chemokines on HIV-1 replication was tested in a neutralization assay. Additionally, the role of cell-to-cell contact between monocytes and CD4+ T cells in the induction of chemokines was studied in a trans-well system.

**Results:** At supra-homeostatic concentrations, IL-7 is a potent inducer of anti-HIV chemokines starting at 48-hours post-treatment. Neutralization of CCL3, CCL4, and CCL5 increased HIV-1 replication in IL-7-treated cells starting on day 3 post-infection. Trans-well experiments demonstrated that a cross-talk between T cells and monocytes, requiring cell-to-cell contact, is essential for efficient chemokine production by IL-7-stimulated T cells, and that the presence of monocytes is essential for the production of anti-HIV-1 chemokines. An investigation into the mechanism involved in the production of chemokines pointed to activation of JAK/STAT and MAPK signaling pathways.

**Conclusion:** In summary, our data delineate a novel path for T cell-mediated HIV-1 control that does not require full-blown T cell activation, shedding new light on the intricate network of cytokine interactions that regulate HIV-1 control and disease progression.

### 237 THE COMPLEMENT PATHWAY IS ACTIVATED IN HIV AND ASSOCIATED WITH NON-AIDS COMORBIDITY

Ivan Vujkovic-Cvijin<sup>1</sup>, Ornella Sortino<sup>1</sup>, Eveline Verheij<sup>2</sup>, Ferdinand W. Wit<sup>2</sup>, Neeltje A. Koestra<sup>2</sup>, Brian Sellers<sup>1</sup>, Maarten Schim van der Loeff<sup>2</sup>, Yasmine Belkaid<sup>1</sup>, Peter Reiss<sup>2</sup>, Irini Sereti<sup>1</sup>

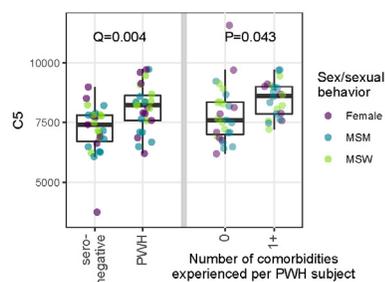
<sup>1</sup>National Institutes of Health, Bethesda, MD, USA, <sup>2</sup>University of Amsterdam, Amsterdam, Netherlands

**Background:** Effective antiretroviral therapy (ART) has extended the lifespan of people with HIV (PWH), who increasingly experience non-AIDS comorbidities which affect their overall health and contribute to early mortality. Occurrence of these comorbidities has been linked to elevated levels of systemic inflammation. Numerous clinical biomarkers including CRP, IL-6, and sCD14 have been shown to be independently associated both with comorbidity prevalence and early mortality. The precise immune pathways involved in the pathogenesis of these inflammatory non-infectious complications, however, remain poorly understood hampering targeted interventions. We hypothesized that unbiased serum proteomics would identify novel pathways enriched in PWH and associated with non-AIDS comorbidities.

**Methods:** Single time point plasma samples from a subset of participants of the AGEHIV Cohort Study were subjected to aptamer-based proteomic screens (SOMAscan), yielding quantification of 1,317 serum proteins. A total of 78 participants were selected including 51 people with HIV (PWH) and 27 seronegative controls (HC) matched for sex/sexual behaviour, age, BMI, and smoking status. Comorbidities captured included non-AIDS defining cancers, myocardial infarction, angina pectoris, ischemic stroke/transient ischemic attack, peripheral arterial disease, heart failure, chronic obstructive pulmonary disease, type 2 diabetes, advanced liver fibrosis, osteoporotic fracture, and renal insufficiency.

**Results:** The median age for both PWH and HC was 55.3 years and 33% of participants were women. The median CD4 count in PWH was 815 cells/uL and all were virologically suppressed. We found that complement activation was the most enriched pathway in the serum proteome of PWH by two independent pathway classification databases (WikiPathways and Human Phenotype Ontology). Complement component C5 was among the top most enriched specific proteins in PWH and correlated significantly with having experienced a clinical non-AIDS event among PWH. C5 retained its significant association with comorbidity prevalence after adjustment for IL-6, D-dimer, suPAR, and sCD14 levels ( $P=0.043$ , OR per 1 IQR = 1.73), and did not correlate with these marker levels.

**Conclusion:** We propose that complement pathway components like C5 should be further evaluated as predictive biomarkers for HIV-associated non-infectious comorbidities. If validated, they may serve as more informative end points in clinical trials, and novel targets for new therapeutic approaches.



### 238 DIGITAL SPATIAL PROFILING OF FIBROTIC LYMPH NODE MICROENVIRONMENTS IN CHRONIC HIV

Brooks Mitchell<sup>1</sup>, Jingjing Gong<sup>2</sup>, Hugh Luk<sup>3</sup>, Nancy Hanks<sup>1</sup>, Dominic C. Chow<sup>1</sup>, Fredrick Yost<sup>1</sup>, Lishomwa Ndhlovu<sup>4</sup>, Owen Chan<sup>3</sup>, Cecilia M. Shikuma<sup>1</sup>

<sup>1</sup>University of Hawaii, Honolulu, HI, USA, <sup>2</sup>NanoString Inc., Seattle, WA, <sup>3</sup>University of Hawaii Cancer Center, Honolulu, HI, <sup>4</sup>Weill Cornell Medicine, New York, NY, USA

**Background:** Characterizing the cellular microenvironment of fibrotic regions in lymph nodes (LN) may further our understanding of LN fibrosis during chronic HIV disease.

**Methods:** Inguinal LN excisions were done by a board-certified surgeon on 6 virally-suppressed persons living with HIV (PLWH) on ART and 4 HIV-uninfected participants (controls) recruited at the University Clinics at Kaka'ako at the John A. Burns School of Medicine. A portion of each LN was formalin-fixed, paraffin-embedded (FFPE) and slide-mounted tissue sections were prepared. H&E staining was performed on LN slides and fibrotic regions were quantified by a board-certified pathologist. Digital spatial profiling (DSP) was performed on LN slides (NanoString Inc.) using the GeoMx DSP platform. LN slides were stained with fluorescent antibodies targeting CD3, CD8, and CD68 to identify cells of interest (COI): CD8 and CD4 T cells and macrophages (M $\phi$ ). Two fibrotic and two non-fibrotic regions were identified for each LN slide remotely by a board-certified pathologist and protein expression profiling for each COI in each region was performed using nCounter barcoding technology. Statistical analyses performed were T-tests and Linear Mix Model tests.

**Results:** LNs excised from PLWH had slightly higher amounts of fibrosis as compared to controls (HIV+ vs. HIV- median LN fibrosis: 25% vs. 18%), however not statistically different ( $p=0.511$ ). Although we did not observe significant fold change (log2FC) differences in protein expression profiles in each LN COI between PLWH and controls, we did find significant log2FC in protein expression profiles in each LN COI between fibrotic and non-fibrotic regions in both groups. In PLWH: M $\phi$  in fibrotic LN regions had a higher protein profile of CD14 (log2FC=1.035;  $p=0.001$ , FDR=0.037), B7-H3 (log2FC=0.728;  $p=0.012$ , FDR=0.119),  $\alpha$ -SMA (log2FC=0.439;  $p=0.035$ , FDR=0.216), and CD163 (log2FC=1.372;  $p=0.045$ , FDR=0.233); CD8 T cells had higher OX40L (log2FC=0.905;  $p=0.002$ , FDR=0.009), fibronectin (log2FC=1.247;  $p=0.006$ , FDR=0.020), and CD34 (log2FC=1.026;  $p=0.009$ , FDR=0.027); CD4 T cells had higher CD34 (log2FC=1.047;  $p=0.005$ , FDR=0.033), fibronectin (log2FC=1.275;  $p=0.005$ , FDR=0.033), OX40L (log2FC=0.880;  $p=0.009$ , FDR=0.034) and B7-H3 (log2FC=0.444;  $p=0.044$ , FDR=0.104). Controls had similar increases in protein profiles for each COI in fibrotic regions.

**Conclusion:** DSP analyses reveal distinct immune cell protein expression profiles in fibrotic LN microenvironments, which may inform targeted fibrosis treatments.

### 239 EFFECT OF HIV ACQUISITION ON SYSTEMIC INFLAMMATION IN A SEROCONVERSION COHORT

Jackson J. Wallner<sup>1</sup>, Ewelina Kośmider<sup>2</sup>, Ana Gervassi<sup>1</sup>, Urvashi Pandey<sup>2</sup>, Delia M. Pinto-Santini<sup>2</sup>, Rachel A. Bender Ignacio<sup>2</sup>, Paul T. Edlefsen<sup>2</sup>, Ann C. Duerr<sup>2</sup>, Lisa M. Frenkel<sup>1</sup>

<sup>1</sup>Seattle Children's Research Institute, Seattle, WA, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA

**Background:** Despite effective antiretroviral therapy (ART), systemic inflammation is reported in people living with HIV (PLWH) compared HIV-uninfected controls. This has been attributed to residual HIV replication, bacterial translocation, coinfections, and side effects of ART.

**Methods:** The Sabes study followed 2109 uninfected high-risk Peruvian men-who-have-sex-with-men and transgender women with monthly HIV testing by serology and PCR. Participants with incident HIV were randomized to initiate

ART immediately or to defer for 24 weeks. Biomarkers (sCD14, sCD163, SuPAR, IFN $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-8, IL-10, IP-10, Leptin, MCP-1, TNF- $\alpha$ , LBP, CRP) were quantitated in plasma at two time points before and two after infection and ART-suppression (>6 months and >12 months after suppression). Stability of each biomarker across the two pre- and the two post-infection/ART-suppression timepoints were assessed across: all participants, by immediate vs. deferred ART arms and by individual; with significance ( $p < 0.05$ ) calculated.

**Results:** Biomarkers were determined for 50 participants (21 randomized to initiate ART immediately and 29 at 24 weeks; with 3 initiating earlier when they met CD4 thresholds for ART in local treatment guidelines). Across the 2 pre-infection timepoints 3 of 15 biomarkers (IP-10, IL-6, CD163) significantly varied, while the others were at steady state. Compared to the pre-infection values, at the first post-infection timepoint, Leptin (n=9/50) and LBP (n=4) decreased and MCP-1 (n=6) increased; with changes in Leptin and MCP-1 observed in both immediate and deferred ART-initiation arms. Comparing levels during ART-suppression to pre-infection timepoints, IFN- $\gamma$  and LBP decreased in the immediate arm, while CRP increased in the deferred arm. During ART-suppression, Leptin and LBP increased and IL-8 decreased in both arms over time. Considering each arm separately, IL-8 decreased, and Leptin significantly increased during ART-suppression for the deferred arm but not for the immediate arm. A sustained increase in  $\geq 2$  pro-inflammatory biomarkers during ART-suppression was not observed in any of the 50 participants.

**Conclusion:** This longitudinal study of PLWH who initiated ART during early infection found little evidence for sustained elevations in pro-inflammatory biomarkers attributable to HIV infection. Instead, elevations of one or a few biomarkers were detected in a minority of participants following infection; biomarkers from before and after infection were stable in most participants.

#### 240 mTOR ACTIVATION LIMITS LPS-INDUCED MONOCYTE INFLAMMATORY AND PROCOAGULANT RESPONSES

Nina Calantone<sup>1</sup>, Hee-kyung Hong<sup>1</sup>, Jason Brenchley<sup>2</sup>, Joseph Bass<sup>1</sup>, Richard T. D'Aquila<sup>1</sup>, Harry E. Taylor<sup>3</sup>

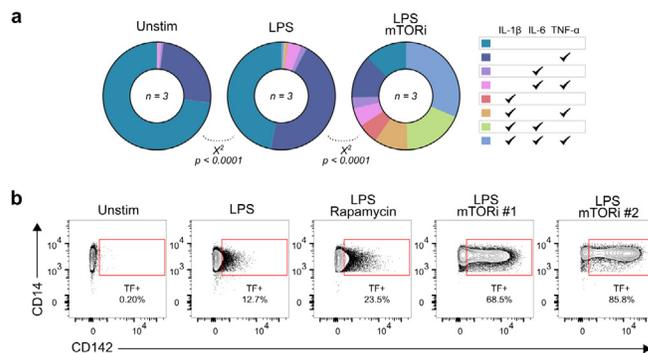
<sup>1</sup>Northwestern University, Chicago, IL, USA, <sup>2</sup>National Institutes of Health, Bethesda, MD, USA, <sup>3</sup>State University of New York Upstate Medical University, Syracuse, NY, USA

**Background:** Microbial translocation and subsequent lipopolysaccharide (LPS) activation of monocytes via TLR4 is likely to increase cardiovascular disease (CVD) risk in persons living with HIV. LPS induces metabolic signaling in monocytes necessary for the production of inflammatory cytokines and a procoagulant, tissue factor (TF). Using primary monocytes, we tested the hypothesis that LPS-induced pro-inflammatory and -coagulant responses are supported by mTOR activity and contribute to CVD risk. Paradoxically, multi-omics analyses here demonstrate that mTOR activates a metabolic pathway that limits abundance of these gene products in monocytes.

**Methods:** Human primary monocytes were treated with LPS in the presence or absence of catalytic mTOR inhibitors (mTORi) and compared with untreated monocytes. Samples were analyzed using both RNAseq and metabolic profiling. Changes in cytokine production were determined by ELISA and intracellular flow cytometry. Phenotypic changes in monocyte activation status and TF expression were also monitored using flow cytometry.

**Results:** Transcriptomic analysis revealed that treatment of primary human monocytes with mTORi potentiates both LPS-induced pro-inflammatory cytokines (IL-1 $\beta$  and IL-6) and coagulation-mediating TF. We found NF- $\kappa$ B-driven transcriptional activity enhances expression of F3 (TF) with LPS stimulation after mTORi treatment. Metabolomic analysis revealed these changes were associated with depletion of NAD<sup>+</sup> levels in mTORi-treated monocytes. The mTORi-mediated increase in TF+ monocytes ex vivo was blunted by NAD<sup>+</sup> precursor supplementation.

**Conclusion:** Collectively, our data support the hypothesis that mTOR signaling checks potentially harmful responses in pro-inflammatory monocytes. Thus, our results are relevant for understanding metabolism-related mechanisms of accelerated pro-inflammatory conditions in PLWH. They also are significant for SARS-CoV-2 infection, which also impairs the gut barrier, depletes NAD<sup>+</sup> pools, and causes coagulopathy. This suggests that the LPS- and mTOR-related mechanisms defined here warrant investigation in SARS-CoV-2 cytokine storm-induced pathogenesis.



**a** PBMC from three independent donors were pretreated with AZD2014, an mTORi, for 6 h and stimulated with LPS (1 ng, 18 h) prior to intracellular cytokine staining and analysis via flow cytometry. **b** Monocytes from three independent donors were pretreated with rapamycin (100 nM) or one of two structurally distinct mTORi (AZD2014 - mTORi #1 and INK128 - mTORi #2, each at 5  $\mu$ M) for 6 h and stimulated with LPS (1  $\mu$ g, 12 h) prior to staining. Data represent gating on leukocyte/singlet/ live/CD14<sup>+</sup>.

#### 241 MONOCYTE SUBSETS AFTER LONG-TERM ART AND MEASURES OF HIV PERSISTENCE IN ACTG A5321

Bernard Macatangay<sup>1</sup>, Deborah McMahon<sup>1</sup>, Hanna Mar<sup>2</sup>, Ronald J. Bosch<sup>2</sup>, Joshua Cyktor<sup>1</sup>, Evelyn Hogg<sup>3</sup>, Luann Borowski<sup>1</sup>, Joseph J. Eron<sup>4</sup>, John W. Mellors<sup>1</sup>, Rajesh T. Gandhi<sup>5</sup>, Charles Rinaldo<sup>1</sup>

<sup>1</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Social & Scientific Systems, Silver Spring, MD, USA,

<sup>4</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>5</sup>Massachusetts General Hospital, Boston, MA, USA

**Background:** Several studies have investigated the role of monocytes in HIV infection, specifically in HIV-associated chronic inflammation. However, it is unclear how these immune cells correlate with measures of HIV persistence in individuals on long-term suppressive ART.

**Methods:** In this cross-sectional study, we determined the frequencies of classical (CD14+CD16<sup>-</sup>), intermediate (CD14+CD16<sup>+</sup>), and non-classical (CD14dimCD16<sup>+</sup>) monocytes in ACTG A5321 participants at study entry using flow cytometry. We also obtained plasma levels of pro- and anti-inflammatory markers by ELISA and multiplex assays. We measured levels of residual plasma HIV RNA and, in CD4+ T cells, HIV DNA, cell-associated HIV (CAR), and intact proviral DNA (IPD) by PCR assays. Spearman correlations were used to assess associations between continuous measures and were adjusted for age, sex, pre-ART RNA and CD4+ T cell count, and years on ART.

**Results:** Participants (N=225) had median age of 49 years, median pre-ART CD4 and CD4 at study entry of 255 and 681 cells/uL, respectively, median pre-ART HIV RNA of 4.6 log<sub>10</sub> cps/mL, and median of 7 years on suppressive ART. Median frequency of classical monocytes was 84.6% (IQR 79.1, 88), intermediate monocytes was 1.4% (0.9, 2.6), and non-classical monocytes was 1.3% (0.6, 2.3). After adjusting for potential confounders, none of the monocyte subset frequencies correlated with HIV DNA, CAR, or residual plasma HIV RNA (-0.08  $\leq r \leq 0.08$ ). Similarly, frequencies of the subsets were not associated with IPD (N=24). Frequencies of classical monocytes modestly correlated with plasma levels of pro-inflammatory markers IL-6 (0.17,  $p=0.01$ ), CCL2 ( $r=0.30$ ,  $p=0.04$ ), and sCD163 (0.16,  $p=0.02$ ), and negatively correlated with years on ART ( $r=-0.18$ ,  $p=0.01$ ). Higher levels of intermediate monocytes correlated with higher levels IP-10 ( $r=0.14$ ,  $p=0.03$ ) and sCD163 ( $r=0.14$ ,  $p=0.04$ ) and showed a trend for negative correlation with anti-inflammatory IL-10 levels ( $r=-0.26$ ,  $p=0.07$ ). None of the immunologic parameters correlated with frequencies of non-classical monocytes.

**Conclusion:** In this study of virally suppressed people with HIV on long-term ART, monocyte subsets were not associated with measured markers of HIV persistence. Classical and intermediate monocytes had modest associations with levels of inflammation and immune activation. Further studies are needed to define the role that monocyte subsets play in HIV persistence and in inflammation and immune activation.

## 242 IMMUNO-INFLAMMATORY PROFILE OF ADVANCED-HIV-INFECTED PERSONS IN A COVID-19 OUTBREAK

**Alessandra Vergori**<sup>1</sup>, Antonio Boschini<sup>2</sup>, Stefania Notari<sup>1</sup>, Patrizia Lorenzini<sup>1</sup>, Roberta Gagliardini<sup>1</sup>, Paolo Ottogalli<sup>2</sup>, Eleonora Cimini<sup>1</sup>, Pierluca Piselli<sup>1</sup>, Leila Angeli<sup>2</sup>, Andrea Antinori<sup>1</sup>, Chiara Agrati<sup>1</sup>, Enrico Girardi<sup>1</sup>

<sup>1</sup>Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, <sup>2</sup>San Patrignano Medical Centre, Rimini, Italy

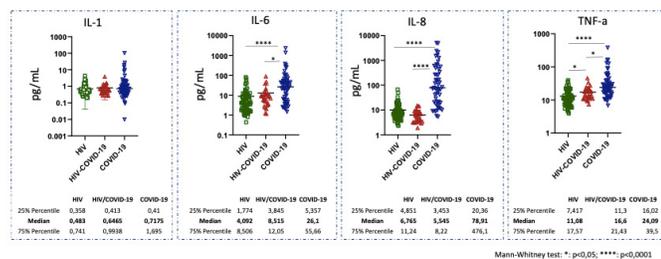
**Background:** It is unclear if chronic immune dysfunction in HIV might affect immune response in COVID-19. Our aim was to analyze the inflammatory profile and the immune response to COVID-19 of a cohort of patients (pts) with a previous AIDS diagnosis and SARS-CoV-2 infection in an assisted living facility in which an outbreak occurred, and to compare them to HIV-negative COVID-19 patients and advanced HIV-positive without COVID-19.

**Methods:** Levels of the inflammatory markers (IL1, IL6, IL8 and TNF $\alpha$ ) were analyzed in advanced HIV+ pts without COVID-19 (group 1), in advanced HIV+ pts infected by SARS-CoV-2 (group 2) along with SARS-CoV-2 specific T-cell response, and in HIV- pts with mild/moderate COVID-19 consecutively hospitalized during the first pandemic wave (group 3). Inflammatory cytokines were quantified by automatic ELISA assay (ELLA system); antibodies titer was evaluated by Elisa assay (Diesse) and SARS-CoV-2 specific T cell response was quantified by Elispot assay. Mann-Whitney was used for comparison between each couple of groups

**Results:** The analysis included group 1 (n=76 pts), group 2 (n=30), group 3 (n=58). Pts of group 1 and 2 did not differ by age, gender and duration of HIV infection. Median CD4 and CD8 was higher in group 2 vs group 1 (348/mm<sup>3</sup> vs 118/mm<sup>3</sup> and 756 vs 518; p<.001). HIVRNA was <50cps/ml in 96.7% of pts in group 2 and 70% in group 1. HIV+/COVID-19 pts had lower prevalence of COVID-19 symptoms than HIV-uninfected COVID-19 comparators (p<.001). Pneumonia was diagnosed in 66% of pts in group 2 and 86% in group 3 (p=0.141), and here was no difference for SpO<sub>2</sub> at COVID-19 diagnosis (p=0.146). 10% of pts in group 2 and 15% in group 3 died during follow-up (p=0.475). Of note, we observed significant higher level of IL6, IL8 and TNF $\alpha$  in group 3 vs group 2 (p<0.05) and group 1 (p<0.0001) (Figure 1). The median time to SARS-CoV-2 clearance was 18 (IQR 16-25) days in group 2, and 12 (IQR 6-23) days in group 3 (p=0.002). Focusing on group 2, 90% of pts showed positive antibodies titers and 100% positive SARS-CoV-2 specific T cell response, suggesting the ability to induce an effective specific immunity.

**Conclusion:** These preliminary results suggest that HIV infection, even in advanced stage, did not seem to negatively impact on COVID-19-related inflammatory state. Moreover, specific immune response in these patients did not differ than that observed in HIV-negative COVID-19 pts. Further investigations are needed to better define the interplay between HIV and SARS-CoV-2.

**Figure 1.** Plasmatic IL-1, IL-6, IL-8 and TNF- $\alpha$  were quantified in HIV (green circles), HIV-COVID-19 (red circles) and in COVID-19 (blue circles) subjects by ELISA assays. Each dot represents one single subject and the horizontal bar identifies the median of values for each cytokine. The details of the median and IQRs are also shown.



## 243 mTOR REGULATION OF ANTIGEN-SPECIFIC CD4+ T-CELL RESPONSES IN MYCOBACTERIAL IRIS

**Luxin Pei**<sup>1</sup>, Chun-Shu Wong<sup>1</sup>, Frances Galindo<sup>1</sup>, Megan Anderson<sup>1</sup>, Elizabeth Laidlaw<sup>1</sup>, Joseph Rocco<sup>1</sup>, Adrian Zelazny<sup>1</sup>, Andrea Lisco<sup>1</sup>, Maura Manion<sup>1</sup>, Irini Sereti<sup>1</sup>

<sup>1</sup>National Institutes of Health, Bethesda, MD, USA

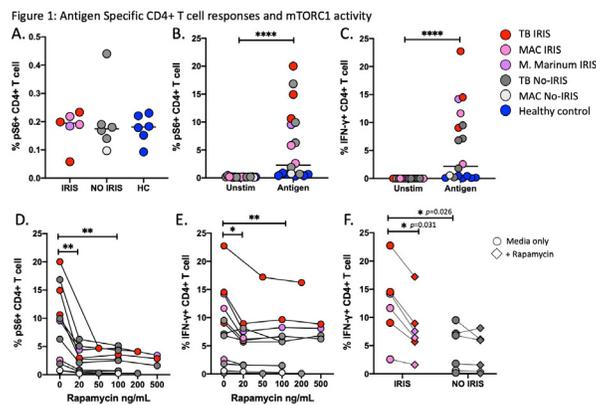
**Background:** Immune reconstitution inflammatory syndrome (IRIS) is an aberrant inflammatory complication observed in HIV+ individuals following the initiation of antiretroviral therapy (ART) frequently associated with mycobacterial co-infections. IRIS is characterized by dysregulated antigen specific CD4+ T cell responses against the opportunistic pathogen. T cell activation is dependent on metabolic reprogramming and the central cell

metabolism pathway, mammalian target of rapamycin (mTOR), can regulate T cell effector function. We hypothesized that mTOR activation is associated with the robust antigen specific CD4+ T cell responses in IRIS and the mTOR pathway could be targeted for therapeutic measures.

**Methods:** Cryopreserved PBMCs at the IRIS event or equivalent time point after ART from 6 HIV+ patients with mycobacterial-IRIS (mycobacterium tuberculosis [MTB], M. avium complex [MAC], and M. marinum) and 6 HIV+ patients with mycobacterial infection (MTB and MAC) who did not develop IRIS were stimulated for 16 hours with mycobacterial antigen (PPD and heat inactivated MAC). mTORC1 inhibitor rapamycin (20-500ng/mL) was added at the beginning of stimulation. Intracellular IFN- $\gamma$  and mTOR downstream target phosphorylated S6 (pS6) were detected using flow cytometry after stimulation.

**Results:** Under unstimulated condition, pS6 expression in CD4+ T cells was low with no difference between IRIS, no-IRIS, and healthy control groups (Figure 1A). Following mycobacterial antigen stimulation, IFN- $\gamma$  production and pS6 level were significantly increased (p<0.0001) in CD4+ T cells in HIV+ patients with mycobacterial co-infection (Figure 1B, C). Rapamycin reduced pS6 expression and IFN- $\gamma$  production in CD4+ T cells in a concentration independent manner (Figure 1D, E). When comparing IRIS with no-IRIS groups, IFN- $\gamma$  producing CD4+ T cells in all IRIS patients were significantly decreased (p=0.031) in the presence of low concentrations of rapamycin at 20-50ng/mL (Figure 1F) reaching plateau at higher concentrations. The effect of rapamycin on IFN- $\gamma$  production in CD4+ T cells after stimulation was not statistically significant in HIV+ no-IRIS patients (Figure 1F).

**Conclusion:** Increased mTOR activity was observed in CD4+ T cell following antigen stimulation in HIV+ patients with mycobacterial co-infection. Rapamycin can successfully reduce pS6 levels and IFN- $\gamma$  production in CD4+ T cells from patients with IRIS following antigen stimulation, which highlights the potential of mTOR pathway as a therapeutic target for IRIS.



## 244 IMPACT OF FATTY ACIDS ON T-CELL FUNCTION AMONG PEOPLE LIVING WITH HIV

**Omkar Chaudhary**<sup>1</sup>, Shihao Xu<sup>2</sup>, Syim Salahuddin<sup>1</sup>, Laurie Andrews<sup>1</sup>, Susan Kaech<sup>2</sup>, Brinda Emu<sup>1</sup>

<sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>Salk Institute for Biological Sciences, La Jolla, CA, USA

**Background:** HIV-infected patients have increased incidence of metabolic disorders with aberrant lipid profiles, due to both HIV itself as well as antiretroviral treatment. The contribution of lipid exposure on the function of T cells in HIV has not been explored.

**Methods:** Measurement of metabolic parameters including lipid and fatty acid (FA) stores, FA transporter (CD36) levels, and T cell inhibitory receptor expression was performed by flow cytometry among HIV-infected (n=35) and uninfected (n=5) subjects. The impact of FA exposure (oleic or linoleic acid) with or without CD36 inhibitor, sulfo-N-succinimidyl oleate (SSO), was measured after stimulation of PBMCs with staphylococcal enterotoxin B (SEB).

**Results:** HIV-infected subjects had higher expression of CD36 on CD8+ T cells compared to healthy individuals (53.4% vs 26%, p=0.03). In HIV-infected subjects, among CD8+CD36+ T cells, the majority were effector memory (37.4%), followed by naïve (20.0%), TEMRA (19.9%) and central memory (12.9%) subsets (p<0.001 for all comparisons). CD8+CD36+ T cells have higher expression of immune inhibitory receptors PD-1 (MFI 260 vs. 152; p<0.01) and CD244 (MFI 375 vs 239; p<0.01) compared to CD36- T cells. CD8+CD36+ cells

had higher levels of FA stores (C12 and C16) compared to CD36- cells ( $p=0.01$  and  $p=0.03$ ), but comparable neutral lipid stores. Upon exposure to oleic acid, CD8+ T cells demonstrated  $96.4\pm 1.5\%$  and  $98.0\pm 2.1\%$  reduction in TNF- $\alpha$  and IFN- $\gamma$  production in response to SEB stimulation, compared to cells not exposed to oleic acid ( $p<0.01$  for both). Though exposure to fatty acids almost completely eliminated cytokine production, exposure to SSO (CD36 inhibitor) restored TNF- $\alpha$  and IFN- $\gamma$  production to  $84.3\pm 9.8\%$  and  $86.5\pm 5.2\%$  of baseline levels respectively. Linoleic acid exposure produced similar results to oleic acid.

**Conclusion:** These data suggest that CD36-mediated FA transport may contribute to T cell dysfunction and compromise function of CD8+ T cells in HIV infection. Future studies to elucidate altered fatty acid metabolism, fatty acid transport, and signaling pathways are needed to provide insight on T cell exhaustion in HIV infection, and clinical impact in non-AIDS related conditions.

#### 245 EFFECT OF HIV ON THE DISTRIBUTION OF NK CELL SUBSETS AND THEIR PHENOTYPE IN INFANTS

Vinh B. Dinh<sup>1</sup>, Stefano Rinaldi<sup>1</sup>, Suresh Pallikkuth<sup>1</sup>, Lesley D. Armas<sup>1</sup>, Nadia Siteo<sup>2</sup>, Rajendra Pahwa<sup>1</sup>, Nicola Cotugno<sup>3</sup>, Paula Vaz<sup>4</sup>, Paolo Palma<sup>3</sup>, Maria Grazia Lain<sup>4</sup>, Savita G. Pahwa<sup>1</sup>

<sup>1</sup>University of Miami, Miami, FL, USA, <sup>2</sup>Instituto Nacional de Saúde, Maputo, Mozambique, <sup>3</sup>Bambino Gesù Children's Hospital, Rome, Italy, <sup>4</sup>Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique

**Background:** NK cells during early life exhibit a distinct phenotype and function that may impact their ability to control HIV infection. Previous studies in perinatally HIV infected children showed alterations in the NK cell compartment when compared to HIV Exposed and Unexposed Uninfected children. This study was performed to investigate the effect of HIV infection on the phenotype of NK cells in neonates prior to ART initiation and its association with Pre-ART plasma HIV viral load (VL).

**Methods:** In a cohort of 33 untreated HIV Infected (HIV) and 35 HIV Exposed Uninfected (HEU) infants (age range 1-2months) from Maputo (Mozambique), we performed in depth phenotypic analysis using a 28 color flow cytometry panel to identify NK cell subsets based on CD56 and CD16 expression such as the cytokine producers (CD56++CD16-, Cyp) and cytotoxic (CD56+CD16+, CTX). NK subsets were further analyzed for the expression of markers of immune activation (IA), immune regulation and trafficking, and compared between HIV and HEU by Mann-Whitney t-test and correlated with VL in HIV by Pearson correlation test.

**Results:** HIV showed an altered distribution of NK cell subsets with a lower frequency of Cyp NK ( $p\leq 0.001$ ) and higher frequency of CTX NK ( $p\leq 0.05$ ) compared to HEU. However, IA of these subsets was increased in HIV as demonstrated by the higher frequency and MFI of the IA marker CD38 and chemokine receptor CCR5 ( $p\leq 0.05$ ). Moreover, frequency of the CD38+ CTX NK cells and MFI of CCR5 in Cyp NK cells showed a positive association with VL ( $p=0.05$   $r=0.4$  and  $p=0.004$   $r=0.6$ , respectively). The frequency and MFI of the inhibitory receptor NKG2A was lower compared to HEU ( $p\leq 0.05$ ) in both subsets but no associations with VL was observed. Finally, within the CTX NK, there was an altered distribution of the co-stimulatory marker CD2 and the immune checkpoint marker TIGIT with HIV showing higher frequency CD2+TIGIT- cells ( $p\leq 0.01$ ) and lower frequency of CD2-TIGIT+ cells ( $p\leq 0.01$ ). No significant correlations were observed between these subsets and VL.

**Conclusion:** The data suggests that NK cells from HIV infants have a more immune activated and mature profile seen in the higher proportion of CTX NK, increased IA markers and reduction of the inhibitory receptor NKG2A. Interestingly, only IA showed significant correlation with plasma VL. These observations highlight the need to investigate the effect of HIV on the development and function of NK cells during early life and their role in HIV viral reservoir establishment.

#### 246 EFFECT OF HIV ON IMMUNE ACTIVATION AND EXHAUSTION IN CD4 AND CD8 T CELLS IN INFANTS

Stefano Rinaldi<sup>1</sup>, Vinh B. Dinh<sup>1</sup>, Suresh Pallikkuth<sup>1</sup>, Lesley D. Armas<sup>1</sup>, Nadia Siteo<sup>2</sup>, Rajendra Pahwa<sup>1</sup>, Nicola Cotugno<sup>3</sup>, Paula Vaz<sup>4</sup>, Paolo Palma<sup>3</sup>, Maria Grazia Lain<sup>4</sup>, Savita G. Pahwa<sup>1</sup>

<sup>1</sup>University of Miami, Miami, FL, USA, <sup>2</sup>Instituto Nacional de Saúde, Maputo, Mozambique, <sup>3</sup>Bambino Gesù Children's Hospital, Rome, Italy, <sup>4</sup>Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique

**Background:** CD4 T cells are the major immune cell subset for the latent HIV reservoir while CD8 T cells are known to be important in controlling the HIV

infection. However, distinct features of the developing infant immune system may impact the establishment of reservoir, as well as the potential for its elimination. In this regard, naïve CD4 T cells were recently suggested as an important CD4 T cell subset for HIV infection and persistence in infants as they account for almost 90% of the whole CD4 T cell population. In this study, we aimed to characterize the phenotypic differences of T cells in a cohort of HIV+ perinatally infected infants before ART initiation to understand the immune milieu in which the HIV reservoir is established.

**Methods:** In a cohort of 33 HIV perinatally Infected (HIV) and 35 HIV Exposed Uninfected (HEU) infants (age range 1-2months) from Maputo (Mozambique), we performed in depth immune phenotypic analysis using a 28 color flow panel to evaluate immune activation and immune exhaustion markers in CD4 and CD8 T cells and maturation subsets before ART initiation. Additionally, naïve CD4 T cells were divided into CD31+ and CD31- subsets, a marker for recent thymic emigrants and null/low proliferation, respectively.

**Results:** Immune Activated (HLA-DR+CD38+) CD4 and CD8 T cells were higher ( $p<0.001$  and  $p<0.0001$  respectively) in HIV infants compared to HEU but no correlation with pre-ART viral load (VL) was observed. The frequency of PD-1 on total CD8 was higher ( $p<0.0001$ ) in HIV, and a positive association with pre-ART VL was found ( $p=0.05$ ,  $r=+0.4$ ). Frequency of circulating T follicular helper cells (Tfh, CD27+CD45RO+CXCR5+) was lower in HIV ( $p<0.05$ ) but proportions of Tfh expressing CD38, HLA-DR, CD25, ICOS and TIGIT were greater. Notably, within the Naïve CD4 T cells, HIV showed a different distribution of CD31 compared to HEU with higher proportion of CD31+ and lower CD31-. Moreover, these 2 subsets were affected differently by HIV infection with CD31+ Naïve showing higher expression of activation markers (CD25, HLA-DR and PD-1) when compared to HEU, while no differences were observed in CD31- Naïve CD4 T cells.

**Conclusion:** The data demonstrate that HIV infection induces a generalized immune activation in both CD4 and CD8 T cells and in their maturational subsets within the first 2 months of life prior to ART initiation. Circulating Tfh and Naïve CD31+ CD4 were the most affected subset by HIV infection in infants which may impact reservoir establishment and HIV persistence.

#### 247 T-CELL IMMUNE DYSREGULATION AND MORTALITY IN WOMEN WITH HIV

Brandilyn A. Peters<sup>1</sup>, Jee-Young Moon<sup>1</sup>, David B. Hanna<sup>1</sup>, Olaf Kutsch<sup>2</sup>, Margaret Fischl<sup>3</sup>, Caitlin A. Moran<sup>4</sup>, Adaora Adimora<sup>5</sup>, Stephen Gange<sup>6</sup>, Nadia Roan<sup>7</sup>, Katherine G. Michel<sup>8</sup>, Michael Augenbraun<sup>9</sup>, Anjali Sharma<sup>1</sup>, Alan Landay<sup>10</sup>, Seema Desai<sup>10</sup>, Robert Kaplan<sup>1</sup>

<sup>1</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>2</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>3</sup>University of Miami, Miami, FL, USA, <sup>4</sup>Emory University, Atlanta, GA, USA, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>7</sup>University of California San Francisco, San Francisco, CA, USA, <sup>8</sup>Georgetown University, Washington, DC, USA, <sup>9</sup>State University of New York Downstate Medical Center, Brooklyn, NY, USA, <sup>10</sup>Rush University, Chicago, IL, USA

**Background:** Dysregulation of adaptive immunity is a hallmark of HIV infection that persists even on antiretroviral therapy (ART), and may contribute to higher risk of non-HIV-related diseases in people with HIV compared to people without HIV. Yet few large, prospective studies with long follow-up have examined associations of adaptive immunity deficits with mortality in HIV.

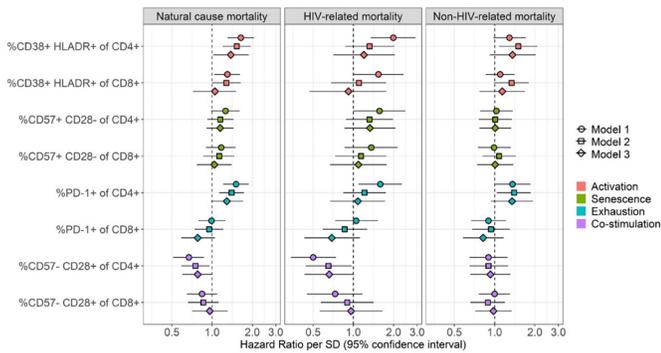
**Methods:** Multiparameter flow cytometry was applied to peripheral blood mononuclear cells from 612 women with HIV in the Women's Interagency HIV Study (WIHS). Samples were collected from 2002-2005, and underlying cause of death ascertained from the National Death Index up to 2018. Using competing risk regression, we examined associations of CD4+ and CD8+ T-cell activation (%CD38+HLADR+), senescence (%CD57+CD28-), exhaustion (%PD-1+), and co-stimulation (%CD57-CD28+) with natural cause (i.e. all causes except overdose and other external causes), HIV-related, and non-HIV-related mortality. We developed nested models to serially adjust for age, demographic, and behavioral characteristics, cardiometabolic factors, and HIV-related factors.

**Results:** At baseline, participants ranged in age from 35 to 47 (median: 41) and 67% were on ART. Among 104 deaths during median 13.3 years follow-up, 90 were due to natural causes (53 non-HIV-related, 37 HIV-related), 10 to external causes, and 4 were missing cause. Higher activation, senescence, and exhaustion of CD4+ T-cells, activation of CD8+ T-cells, and lower co-stimulation of CD4+ T-cells, were significantly associated with natural cause mortality, adjusting for age, demographic, and behavioral characteristics (Figure 1). Adjustment for cardiometabolic and HIV-related factors attenuated

these associations. This pattern of associations was consistent for HIV-related mortality. For non-HIV-related mortality, only activation and exhaustion of CD4+ T-cells were marginally associated with the outcome, and these were not attenuated by further adjustment. Associations of CD4+ T-cell activation, exhaustion, and co-stimulation with natural cause mortality tended to be stronger in women with uncontrolled HIV (detectable viral load or CD4 cell count <500 cells/mm<sup>3</sup>) vs. controlled HIV, though interactions were not significant.

**Conclusion:** Consistent with HIV pathogenesis, dysregulation in multiple CD4+ T-cell subsets is associated with HIV-related mortality. Activation and exhaustion of CD4+ T-cells may also be involved in non-HIV-related mortality, independent of cardiometabolic or HIV-related factors.

**Figure 1. Adaptive immune markers and mortality in women with HIV.** Competing risk regression was used to assess the associations of CD4+ and CD8+ T-cell activation (%CD38+HLADR+), senescence (%CD57+CD28-), exhaustion (%PD-1+), and co-stimulation (%CD57-CD28+) with natural-cause mortality (i.e. excluding external causes), HIV-related mortality, and non-HIV-related mortality. Immune markers were Z-score standardized; plot shows hazard ratios (95% CI) for one standard deviation increase in the immune markers. Model 1 adjusts for age, study site, race/ethnicity, income, education, crack/cocaine use, injection drug use, alcohol use, smoking, and hepatitis C virus infection. Model 2 adjusts for all Model 1 covariates and BMI, systolic blood pressure, cholesterol, HDL, antihypertension medication, lipid lowering medication, and diabetes. Model 3 adjusts for all Model 2 covariates and CD4 cell count, HIV viral load, antiretroviral therapy, and AIDS.



## 248 IMPACT OF REPRODUCTIVE AGING ON IMMUNE FUNCTION IN CISGENDER MEN AND WOMEN WITH HIV

Stephen A. Rawlings<sup>1</sup>, Antoine Chaillon<sup>1</sup>, Masato Nakazawa<sup>1</sup>, Eileen P. Scully<sup>2</sup>, Brendon Woodworth<sup>1</sup>, Christina Huynh<sup>1</sup>, Christy Anderson<sup>1</sup>, Jonathan Karn<sup>3</sup>, Alan Landay<sup>4</sup>, Sara Gianella<sup>1</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>4</sup>Rush University, Chicago, IL, USA

**Background:** Women represent more than half of all HIV infections.

**Understanding the changes in the immune system during reproductive aging is crucial to inform treatment and cure strategies.**

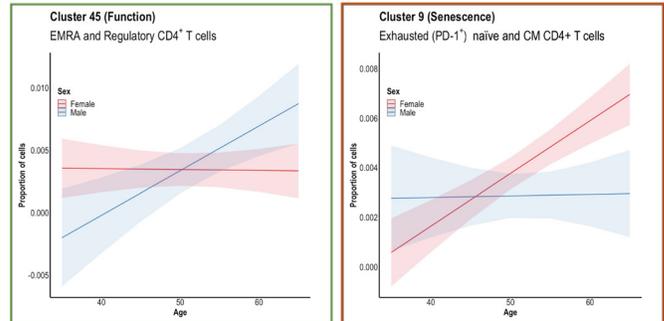
**Methods:** Longitudinal samples (N=415) from virally suppressed cis-gendered women (N=61) and men (N=31) were retrospectively identified from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) population. Participants were aged 40-55 at the time of ART initiation and virally suppressed (<20 copies/ml) throughout the study period. Participants did not report taking hormonal therapy during follow-up. Cryopreserved peripheral blood mononuclear cells were thawed and stained with a panel of fluorescent-tagged antibodies to identify cell populations of interest. Flow cytometric analysis included initial gating for singlet events and cell viability, followed by captured event clustering with the R software package, Phenograph. Immune phenotypes were assigned using a computational algorithm and confirmed manually. Clusters were analyzed longitudinally for significant variability across participants by sex using a linear mixed-effects (LME) model.

**Results:** We identified 327 immune cell clusters including CD4+ (N=64), CD8+ (N=57), double negative CD4-CD8- (N=13), and double positive CD4+CD8+ (N=12) T cells. The remaining 181 clusters remained undefined based on the immune markers included in the panel. LME models identified 54 clusters that significantly differ by sex (median follow up 7.7 years [95%: 2.3-15.1]). The most dynamic T cell cluster was a phenotypic mixture of naïve and central memory with high PD-1 expression (cluster 9), suggesting associated inflammatory responses and functional exhaustion with a possible link to HIV reservoir expansion. This cell subset was increased significantly over time in women, but not in men (Fig.1A). Another dynamic cluster (cluster 45, Fig. 1A) was identified as terminally differentiated effector memory CD4+/regulatory T cells (with

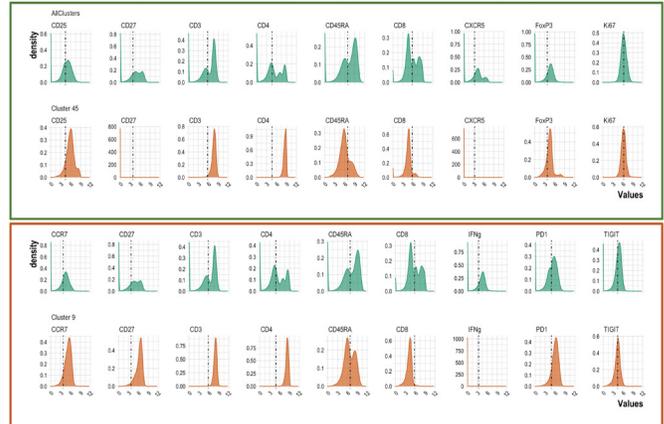
high CD45RA and bimodal FoxP3 expression). In this case, the subset increased significantly over time in men, but not in women. Men also experienced a faster decline in double negative (CD4-CD8-) T cell clusters and double positive T cell clusters.

**Conclusion:** Women have increasing exhausted T cells as they age, whereas men have an increasing population of regulatory type T cells. These changes in immune cell phenotype may be linked to comorbidities associated with sex-specific patterns of inflammaging and HIV persistence.

### A. Cluster dynamics over time



### B. Marker density of selected clusters (in orange) and all clusters (in green)



**Figure Legend:** Two PBMC clusters were identified by a linear mixed-effects model as being the most dynamic between men and women as they age (A). The proportion of cells in the cluster from each participant is plotted against the age of the participant at the time of sampling (cluster 45 on left, cluster 9 on right). Solid lines show best fit and shaded regions 95% confidence intervals for men (blue) and women (red) as participants age. In an effort to identify the type of cells in the cluster, distribution curves of the marker expression in all events analyzed (B, green) were compared to the distribution for that marker in each cluster (B, orange). Vertical dashed lines represent the mean expression of a particular marker for all events analyzed. Phenotypes were inferred by calling markers "positive" or "negative" based on the distribution of marker intensity within a cluster compared to the overall mean line. Cluster 45 is shown above cluster 9.

## 249 EXOSOMES AND VIRUSES: A TALE OF 2 OVERLAPPING WORLDS

Yuriy Kim<sup>1</sup>, Daniel Pinto<sup>1</sup>, Gifty Mensah<sup>1</sup>, Maria Cowen<sup>1</sup>, James Erickson<sup>1</sup>, Heather Branscome<sup>1</sup>, Michelle Pleet<sup>1</sup>, Catherine DeMarino<sup>1</sup>, Renaud Mahieux<sup>2</sup>, Fatah Kashanchi<sup>1</sup>

<sup>1</sup>George Mason University, Fairfax, VA, USA, <sup>2</sup>Centre Hospitalier Universitaire de Lyon, Lyon, France

**Background:** Extracellular vesicles (EVs) play a significant role in intercellular communication by serving as a carrier for the transfer of membrane and cytosolic proteins, lipids, and RNA between cells.

**Methods:** In recent years, using state of art technologies such as RNA seq, RPMA, and single cell omics, we have found that virally infected cells including HIV-1, HTLV-1, Rift Valley Fever, Zika, Ebola, and Coronavirus infected cells secrete exosomes that contain biomarker of these infections in urine, saliva, CSF, and blood. We have been able to separate and characterize EVs from several different viruses including HIV-1.

**Results:** These EVs are not infectious and have a different density than infectious virions using gradients. They contain various viral RNAs including TAR (non-coding RNA), Nef, gp120/160 and Tat. The origin of these EVs are infected cells, especially when treated with cART or Interferons. They are

present in patient samples tested (plasma and CSF, 33%-95%) to date (4 cohorts of 5-20 patients each). The EVs contribute to pro-inflammatory signals in the naïve recipient cells using TLR3 signaling. Recently, we have asked about the timing difference between EV and virus release from infected cells using serum starvation experiments from cells followed by release. Results from supernatants of uninfected cells showed a peak of tetraspanin proteins (CD63, CD81, and CD9) at 6 hours and a gradual decrease of all EV associated proteins by 24 hours. However, the EV from HIV-1 infected cells showed all three tetraspanins present at 3 hours and expression gradually increased up to 24 hours. HIV-1 viral proteins (p24, gp120, Nef) expression was present at 6 hours and continued to increase and peaked at 24 hours. HIV-1 supernatant 6-hour sample was found not to be infectious. However, infectious HIV-1 was successfully rescued from 24-hour sample.

**Conclusion:** Our data indicates that EV release may occur prior to viral release in infected cells, thereby implicating a potentially significant effect of EVs on uninfected recipient cells prior to subsequent viral infection.

**ACKNOWLEDGMENTS:** This work was supported by NIH research grants (R01AI043894, R21AI113140, R21AI114490 to F.K. and F31NS086453). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

## 250 STRAIN-DEPENDENT EFFECTS OF SIGNAL PEPTIDES ON HIV-1 Env GLYCOSYLATION AND FUNCTIONS

**Chitra Upadhyay**<sup>1</sup>, Roya Feyznehad<sup>1</sup>, Liwei Cao<sup>2</sup>, Kun-Wei Chan<sup>3</sup>, Weiming Yang<sup>2</sup>, Hui Zhang<sup>2</sup>, Xiang-Peng Kong<sup>3</sup>, Susan Zolla-Pazner<sup>1</sup>, Catarina E. Hioe<sup>1</sup>  
<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>2</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>3</sup>New York University Langone Medical Center, New York, NY, USA

**Background:** HIV-1 Env glycoprotein is a trimer of heterodimeric gp120 and gp41 subunits that are produced from a gp160 precursor. The N terminus of gp160 contains a signal peptide (SP) which is essential for targeting the nascent protein to the endoplasmic reticulum where the Env SP is cleaved and removed from the maturing Env. Thus, the Env SP is not a part of the mature Env present on the surfaces of virions and infected cells. Nonetheless, similar to the mature Env, the Env SP displays an extraordinary genetic diversity, although its significance is not well understood. This study investigated the influence of SP sequence diversity on Env glycosylation and functions.

**Methods:** We constructed chimeric infectious molecular clones by swapping the native SPs of HIV-1 isolates CMU06 and SF162 with SPs from other HIV-1 isolates (MW965.26, 398F1, CH119, and 271.1). SP-swapped and WT viruses were produced in HEK293T and human peripheral blood mononuclear cells (PBMCs) and evaluated for site-specific glycan contents by mass spectrometry. We also assessed the effects of SP exchanges on DC-SIGN-mediated virus transmission and virus neutralization by monoclonal antibodies (mAbs).

**Results:** Comparison of virion-derived total Envs from SP-swapped viruses vs their respective WT revealed strain-specific alterations in the proportions of oligomannose and complex glycans at many glycosites particularly at the trimer apex and base. Modified glycan compositions were associated with reduced DC-SIGN-mediated transmission of CMU06 but not SF162. Differential effects were also seen on CMU06 vs SF162 sensitivity to neutralization by mAbs targeting different epitopes, including V1V2, V3 and gp41.

**Conclusion:** These data demonstrate the contribution of SP in determining Env glycosylation, virus transmission and antibody recognition in a virus strain-specific manner. Hence, this study provides direct evidence for a critical role of the HIV Env SP in virus-host interaction.

## 251 AN EPIGENETIC ARCHITECTURE THEORY TO ASSESS THE FITNESS OF VIRAL SEQUENCES

**Rocío Carrasco-Hernandez**<sup>1</sup>, Humberto Valenzuela-Ponce<sup>2</sup>, Claudia García-Morales<sup>2</sup>, Margarita Matías-Florentino<sup>2</sup>, Sepideh Mazrouee<sup>1</sup>, Gustavo Reyes-Teran<sup>3</sup>, Santiago Ávila-Ríos<sup>2</sup>, Davey M. Smith<sup>1</sup>, Joel Wertheim<sup>1</sup>  
<sup>1</sup>University of California San Diego, San Diego, CA, USA, <sup>2</sup>Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico, <sup>3</sup>Coordinating Commission of the Mexican National Institutes of Health, Mexico City, Mexico

**Background:** Intrahost viral dynamics are an underlying cause of transmissibility. Architectural studies of viral sequences may retrieve epigenetic information to assess virulence. Nucleotide statistics of a viral sequence –e.g. the proportions of the CpG duplet and the Guanine-Cytosine content (GC) –are 'architectural traits', sequence-independent, and can be achieved similarly by

independent genetic lineages. Among RNA viruses, epigenetic interactions have been reported between viral genomic CpG contents and immune targeting enzymes of the host cell, affecting viral replication. In turn, GC content has been suggested to affect gene expression and evolution rates. We propose that these architectural traits can be coordinates of an n-dimensional space, and space occupancy could predict disease progression measures, such as viral load (VL) and %CD4.

**Methods:** HIV pol sequences obtained for clinical and surveillance purposes in Mexico, Guatemala, Belize, El Salvador, Honduras and Nicaragua between 2014 and 2019 were included. To visualize the effect of architectural occupancy -i.e. space occupancy of viral loads on the CpG/GC plane-, sequences were plotted over an 'Architectural Space' (AS) with two axes: CpG vs. GC. Then, each point was colored and sized according to its associated VL. Higher associated VLs were expected to occupy the bottom-left sections of the AS (i.e. lower CpG and GC). Also, two linear models were built: i)  $\log_{10}(VL) \sim \%CpG + \%GC$ ; and ii)  $CD4 \sim \%CpG + \%GC$ . Slopes were expected negative for both predictors versus VL and, positive versus CD4.

**Results:** We analyzed 4027 HIV-pol sequences. %CpG ranged from 0.01 – 0.7; and %GC, from 35 – 39.3. Higher associated VLs tended to occupy the lower-left sections of the CpG/GC plane (Figure 1). Suggesting a negative effect of both traits on disease progression. R-squared values were: 0.01 for VL and 0.03 for CD4. Significant slopes confirmed visualizations, being negative for  $\log_{10}(VL)$ : -0.06 for GC ( $p < 0.01$ ), and -0.74 for CpG ( $p < 0.001$ ); and, positive for %CD4: 1.75 for GC ( $p < 0.001$ ) and 9.48 for CpG ( $p < 0.001$ ).

**Conclusion:** Linear models returned significant slopes but low R2, suggesting that CpG and GC architectures may significantly explain some of the VL and %CD4 variance; and that AS occupancy could return information on viral fitness not previously identifiable from VL or CD4. Architectural space can expand dimensions, and occupancy of pathogens could become a clinically relevant measure to assess potential virulence and transmissibility.

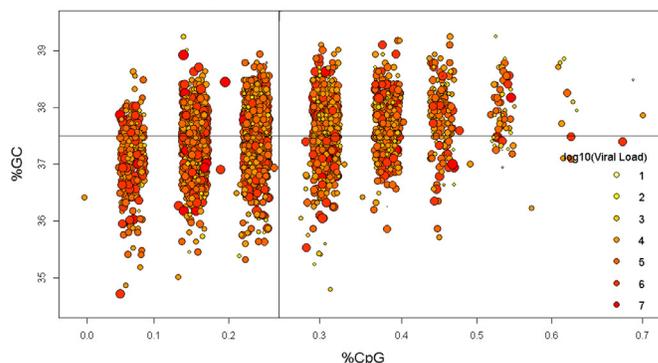


Fig 1 – Architectural space with CpG and GC axes and the distribution of associated VL values represented by color scale and increasing point size

## 252 HIV ACQUISITION PREDICTED BY LOWER BASELINE BUT GREATER INCREASE IN IMMUNE ACTIVATION

**Rachel A. Bender Ignacio**<sup>1</sup>, Sayan Dasgupta<sup>2</sup>, Rogelio Valdez<sup>3</sup>, Urvashi Pandey<sup>2</sup>, Siavash Pasalar<sup>2</sup>, Ricardo Alfaro<sup>4</sup>, Javier R. Lama<sup>5</sup>, Ann C. Duerr<sup>2</sup>  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>4</sup>Universidad Nacional Mayor de San Marcos, Lima, Peru, <sup>5</sup>Impacta Peru, Barranco, Peru

**Background:** Although immune activation is associated with HIV acquisition, the exact high-risk immune profiles and mechanisms are not well understood. Prior studies attempting to answer this question relied on cross sectional samples, most without close proximity to HIV acquisition.

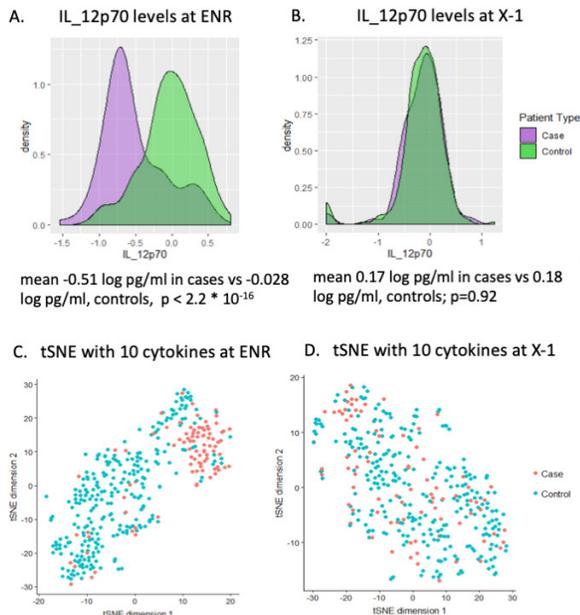
**Methods:** The Sabes study followed 2,109 MSM and transwomen in Lima, Peru with monthly HIV testing (Ab, RNA). We selected 90 cases who acquired HIV during up to 24-month follow-up and 270 controls who did not, matched 3:1 on time under observation. We conducted a panel of 10 plasma immune activation markers using MSD at enrollment (ENR) and at the visit one month prior to first HIV detection in cases, or matched study visit in controls (X-1). We used linear mixed models to associate biomarker levels at ENR, X-1, and between-visit change with HIV acquisition; we used machine learning (LASSO) to select

important biomarkers and covariates, including demographic and behavioral risks factors.

**Results:** The median time between ENR and HIV acquisition for cases was 361 days (IQR 180, 517). For all tested markers except IL-7 (MIP-1, IL-2, IL-6, IL-10, IL-12p70, TNF- $\alpha$ , IP-10, IFN- $\gamma$ , TNF- $\beta$ ) cases had significantly lower values than controls at ENR but were nearly indistinguishable at X-1 (Figure). LASSO selected increase in IP-10, IL-7, IL-12p70, and IL-10 as jointly predictive of HIV acquisition, and relationships of these markers to outcome were modified by younger age, alcohol consumption, sexual role (versatile, receptive), having post-secondary education, and participating in sex work. Sensitivity analyses for time to HIV acquisition and potential for undetected eclipse-phase (HIV RNA-ve) infections at X-1 sampling did not change these results.

**Conclusion:** Unexpectedly, markers of immune activation in persons who acquired HIV in the subsequent month were indistinguishable from controls. However, almost all measured markers were significantly lower at enrollment in those who later acquired HIV; among cases, pre-infection levels in those with the largest increases did not exceed levels in controls at X-1. While changes over time may reflect regression to the mean, this study is novel in revealing that absolute changes in several markers were most predictive of HIV acquisition. This work may support a hypothesis that the process of activation, rather than chronic activation, increases risk. Further analysis of VirScan results in this study is ongoing and may shed light on viral infections that could explain these observations.

#### Differences in markers of immune activation between persons who did or did not acquire HIV



**Figure:** Analysis of 10 cytokines measured by MSD in plasma showed drastic differences in most markers at ENR (A: IL-12p70 as an example), but not between last HIV negative visit or control (B). T-distributed stochastic neighbor embedding (tSNE) plots show overall clustering that visually distinguishes those who did or did not later acquire HIV (at ENR in C) but indistinguishable distributions on average 1 month prior to HIV acquisition vs control visit (D).

#### 253 SINGLE-CELL TRANSCRIPTOME ANALYSIS DURING PRIMARY HIV-1 INFECTION AND cART

**Teresa Evering**<sup>1</sup>, Roshan Sharma<sup>2</sup>, William Stephenson<sup>2</sup>, Leslie St. Bernard<sup>3</sup>, Peter Smibert<sup>2</sup>, Martin Markowitz<sup>4</sup>, Nicolas Robine<sup>2</sup>

<sup>1</sup>Weill Cornell Medicine, New York, NY, USA, <sup>2</sup>New York Genome Center, New York, NY, USA, <sup>3</sup>Aaron Diamond AIDS Research Center, New York, NY, USA, <sup>4</sup>Columbia University Medical Center, New York, NY, USA

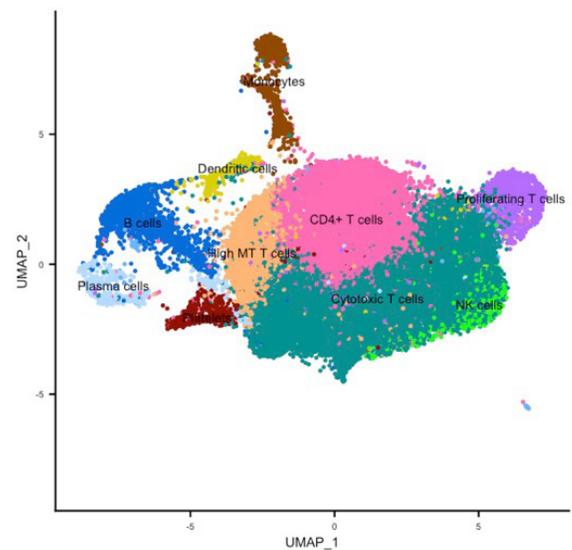
**Background:** Treatment of HIV-1-positive individuals early in the course of infection provides the best opportunity for preservation of host immune function and limits the size of the latent HIV-1 reservoir. However, the transcriptional dynamics of discrete cellular subsets during treatment for primary HIV-1 infection has not been described in detail. We used single-cell

RNA-sequencing to examine cell-type specific changes in gene expression in response to the initiation of cART during primary HIV-1 infection.

**Methods:** Using Drop-seq single-cell profiling, we generated longitudinal, unbiased gene-transcriptional profiles from cryopreserved PBMC of 10 HIV-1 positive MSM presenting during primary HIV-1 infection (TP1) and after approximately 1 year of uninterrupted, suppressive cART with PI or NNRTI based regimens (TP2). Mean age was 36 (24-44) years at initial presentation. Median estimated duration of HIV-1 infection at TP1 was 60 days (30-130). At TP1, individuals had lower median CD4/CD8 T cell ratios (0.47 versus 1.22) and higher HIV-1 RNA levels (Log<sub>10</sub> 5.6 vs. < 1.7) compared to TP2, at which time all individuals were virologically suppressed ( $p < 0.05$  for all comparisons). GSEA identified gene pathways significantly modulated by cART.

**Results:** After strict quality control and filtering, our analysis identified 27,388 cells. The mean read depth per cell was approximately 43,000–84,000 as reported by Cell Ranger. Clustering using Seurat identified 10 clusters using expression of classical cell type markers (Fig 1). We then compared abundance of cell populations and transcriptional profiles within specific cell populations before and after cART initiation. As expected, we identified increases in the CD4/CD8 ratio after cART in all participants. In the CD4+ T cell, cytotoxic T-cell and B-cell compartments, gene pathways significantly down-regulated after cART initiation include inflammatory, complement, interferon- $\alpha$  and interferon- $\gamma$  and the G2/M checkpoint (adj  $p < 0.05$ ). In NK cells, novel significant down-regulation of E2F targets essential for DNA replication and cell cycle progression was also identified.

**Conclusion:** Single-cell transcriptional profiling of cohorts of HIV-1 positive individuals initiating cART during primary infection can provide an immunologic picture of an idealized immune response to cART and identify cell-type specific and global modifiable pathways of immune reconstitution.



#### 254 EARLY ART INITIATION MAY PRESERVE INFLUENZA VACCINE RESPONSE DURABILITY

**Samuel R. Schnittman**<sup>1</sup>, Jordan Boeck<sup>1</sup>, Gabriele B. Beck-Engeser<sup>1</sup>, Haelee Ahn<sup>1</sup>, Norman Jones<sup>1</sup>, Amelia N. Deitchman<sup>1</sup>, Vanessa York<sup>1</sup>, Heather Hartig<sup>1</sup>, Rebecca Hoh<sup>1</sup>, Frederick M. Hecht<sup>1</sup>, Jeffrey N. Martin<sup>1</sup>, Fran Aweeka<sup>1</sup>, Steven G. Deeks<sup>1</sup>, Jeffrey Milush<sup>1</sup>, Peter W. Hunt<sup>1</sup>

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** Aging and immunosenescence predict poor influenza vaccine responsiveness. We sought to determine whether treated HIV is also associated with poor vaccine responsiveness, and if delayed antiretroviral therapy (ART) initiation or persistent immune activation affect vaccine response in this setting.

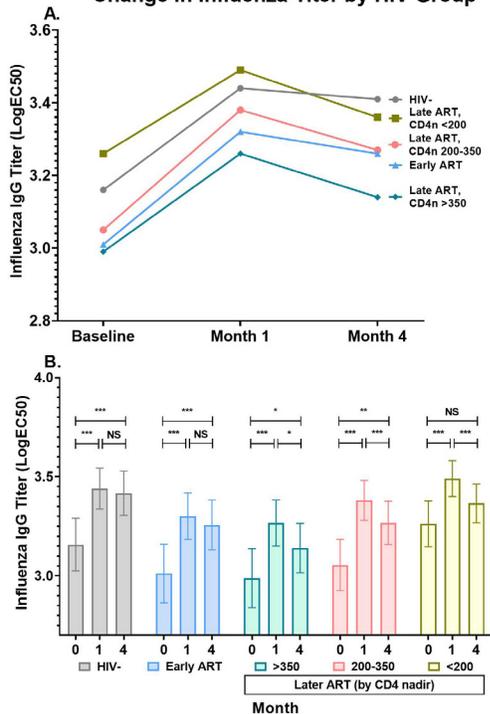
**Methods:** People with HIV (PWH) with ART-mediated viral suppression >1 year and HIV- controls, all CMV+ and enriched for HIV risk factors, received the seasonal flu vaccine 2014-2018. Total IgG titer against each year's vaccine antigens were assessed at baseline, 1, and 4 months (M1 and M4, respectively). PWH were stratified by timing of ART initiation (within 6 months of HIV infection [early ART] vs later), and among later initiators, by nadir

CD4 count (>350, 200-350, <200 cells/ml). Plasma KT ratio, IP-10, sCD14, sCD163, IL-6, sTNFR2, and suPAR were assessed at baseline. Antibody titer changes after vaccination were assessed with linear mixed-models, adjusted for demographics, health-related behaviors, and timepoint-by-group and biomarker-by-timepoint interaction terms.

**Results:** Of 164 PWH and 41 HIV- participants, median age was 54 years and 91% were men. Of the HIV-, 56% were MSM, 34% were current smokers, 15% had distant IDU, and 41% had >100 lifetime male sexual partners. Of the PWH, 34 were early ART initiators, and the remainder had a range of nadir CD4 counts: >350 (n=32), 200-350 (n=43), and <200 cells/ml (n=55). Median duration of viral suppression was 8 years. Flu-specific IgG titers increased from baseline to M1 similarly in all groups. While there was no evidence for titer decay M1 to M4 in HIV- and early ART initiators, later ART initiators experienced significant declines (P<0.04 for all). The extent of titer decay M1 to M4 was impacted by ART initiation timing: compared to HIV-, the early ART group had a similar slope of decay (P=0.66), but the combined later ART groups experienced a significantly greater rate of decline (P=0.02). IP-10 and sCD163, but not other biomarkers, were associated with a 9% greater rate of titer decline M1 to M4 per 1 IQR increase in either biomarker (P=0.05 and P=0.03).

**Conclusion:** ART-suppressed PWH have similar early humoral responses to influenza vaccination compared to HIV- adults, but only those who start ART within 6 months of infection appear to maintain similar response durability at 4 months. While the clinical implications of these findings remain unclear, some immune activation pathways appear associated with shorter response durability.

Change in Influenza Titer by HIV Group



**255 HIV PLASMA VIREMIA IS THE PRODUCT OF ONLY A SMALL PROPORTION OF INFECTED CELLS**

**Elizabeth Anderson**<sup>1</sup>, Shawn Hill<sup>1</sup>, Catherine Rehm<sup>2</sup>, Lindsey Adams<sup>1</sup>, Erin Madeen<sup>1</sup>, Mary E. Zipparo<sup>1</sup>, Thuy Nguyen<sup>1</sup>, Mary F. Kearney<sup>1</sup>, Robert Gorelick<sup>3</sup>, John M. Coffin<sup>4</sup>, Frank Maldarelli<sup>1</sup>

<sup>1</sup>National Cancer Institute, Frederick, MD, USA, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>3</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA, <sup>4</sup>Tufts University, Boston, MA, USA

**Background:** HIV persistence during combination antiretroviral therapy (ART) is the principal obstacle to HIV cure. Determining the dynamics of infected cells prior to ART is essential to understanding the kinetics of reservoir seeding and persistence during therapy. Although the decay rate of productively infected cells has been well described, the numbers of cells infected daily and the levels of HIV RNA they produce has not been extensively investigated. To address this

issue, we used sensitive droplet digital PCR (ddPCR) and single infected cell analyses to quantify early HIV decay kinetics.

**Methods:** HIV infected ART-naïve subjects (N=8, 7 male) underwent ART in natural history trials at NIH. HIV cell associated (ca) DNA from peripheral blood lymphocytes (PBLs) prior to and after 6 days of ART was quantified using ddPCR assays targeting the LTR, and the numbers of cells infected daily were estimated from the numbers of infected cells lost during the 6-day interval. Plasma HIV RNA was measured (bDNA) frequently during this period. HIV caRNA was quantified for a subset (N=3) using qPCR of HIV gag in single infected cells obtained by end point dilution. Standard mathematical models were used to determine half-lives, HIV RNA production per cell, and reproductive ratio (R0).

**Results:** Only a small fraction of all HIV DNA positive cells detected in PBLs were lost per day after ART initiation, from which we estimated an average of 8.5 x 10<sup>7</sup> cells infected/day/individual (range 5.0-13 x 10<sup>7</sup>). From the >40-fold decay of viremia during the first week of therapy, we estimated median daily virus production of 5.1 x 10<sup>not3</sup> virions/cell and R0 of 47 (range 12-92). Single infected cell analysis revealed that, prior to ART, 71-84% of all DNA positive cells produced HIV RNA; the majority containing c. 3 copies; a minority (1-1.8%) were "high-expressors" with 25-303 copies HIV RNA/cell. After 6 days of ART, only 17-21% of HIV DNA-containing cells contained HIV RNA, and levels of high expressors declined markedly. The half-life of high expressing cells (1.8 d) was similar to that of HIV producing cells measured independently by analyzing decay of plasma viremia (1.2 d).

**Conclusion:** The numbers of cells infected daily is a small fraction of all HIV DNA positive cells. A small fraction of all RNA positive cells contain high HIV RNA copy numbers and have a short half-life suggesting that these high expressing cells in peripheral blood are responsible for producing plasma viremia.

**256 NEUTRALIZING-ANTIBODY RESPONSES FOLLOWING SARS-CoV-2 INFECTION**

**Juan M. Tiraboschi**<sup>1</sup>, Sofia Scevola<sup>2</sup>, Julià Blanco<sup>3</sup>, Laura Calatayud<sup>2</sup>, Paula Prieto<sup>2</sup>, Irene Soriano<sup>2</sup>, Laura Arregui<sup>1</sup>, Xavier Solanich<sup>2</sup>, Arnau Antolí<sup>2</sup>, Arkaitz Imaz<sup>2</sup>, María Saumoy<sup>1</sup>, Ana Silva<sup>2</sup>, Edwards Pradenas<sup>3</sup>, Jordi Carratala<sup>2</sup>, Daniel Podzaczner<sup>2</sup>

<sup>1</sup>Hospital Universitari de Bellvitge, Barcelona, Spain, <sup>2</sup>Bellvitge University Hospital, Barcelona, Spain, <sup>3</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>4</sup>Bellvitge Biomedical Research Institute, Barcelona, Spain

**Background:** Understanding the adaptive immune response to SARS-CoV-2, kinetics, persistence and their relationship with the disease severity would be crucial in order to predict recurrences, reinfections and could serve in the design of vaccination strategies. We sought to characterize IgG and neutralizing antibodies (NAbs) against SARS-CoV-2 in patients who were admitted to hospital with COVID-19 disease.

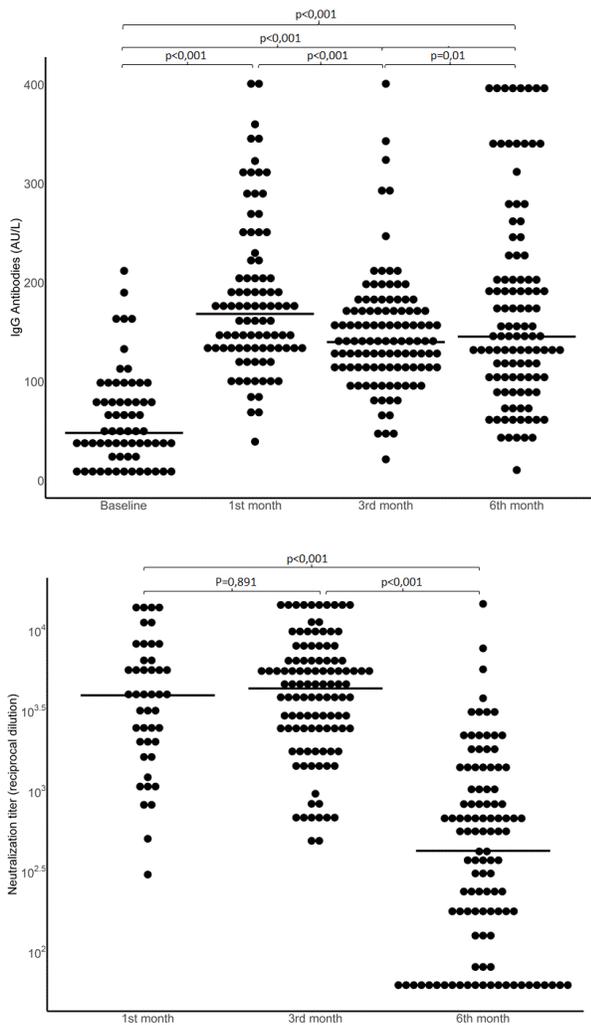
**Methods:** All patients admitted between March-April 2020 with moderate, severe and critical SARS-CoV-2 pneumonia were prospectively studied. Clinical, laboratory data and IgG against SARS-CoV-2 levels were assessed at baseline (upon admission) and months 1, 3 and 6. NAbs were assessed at month 1, 3 and 6. IgG against the SARS-CoV-2 spike (S) protein was measured in serum by chemiluminescence (LIAISON® SARS-CoV-2 S1/S2, DiaSorin) and results were expressed in arbitrary units (AU)/mL. The neutralizing activity of plasma samples was analyzed in a 293T/hACE2 cell infection test using a surrogate viral inhibition assay that uses human immunodeficiency virus type 1 (HIV-1)-based virus expressing SARS-CoV-2 S protein and Luciferase. For neutralization assays, pseudoviruses were incubated with increasing plasma dilutions (range 1/60 - 1/14,580) in order to obtain the ID50 values.

**Results:** A total of 110 patients who were discharged from hospital were recruited. Median (range) age was 61 (57-71); 61.2% were male and most reported comorbidities were hypertension (39.6%), diabetes (24.3%) and obesity (19.8%). Median time from symptoms onset to admission was 9 days (range 7-11). Median (range) IgG levels (AU/mL) at baseline and months 1, 3 and 6 were 48 (28-81), 168 (134-210), 140 (112-171) and 146 (104-206) respectively. No significant differences were observed in median IgG fold change values up to month 6 among severity groups. Median (range) ID50 values for NAbs at months 1, 3 and 6 were 3938 (1958-6407), 4344 (2335-6752) and 424 (124-1022) respectively. NAb titers presented a significant decrease (overall -10.2-fold change from maximal values) without differences among severity groups (Figure 1 a and b). No reinfections occurred.

**Conclusion:** Specific humoral immune response to SARS CoV-2 in patients requiring hospital admission characterizes for a clear peak between 30 and 90

days after admission followed by a significant decline in titer of NAb by day 180 regardless of disease severity. Longer follow-up may help to determine the longevity of the specific immune response.

Fig 1. a) IgG antibodies and b) NAb at different time points.



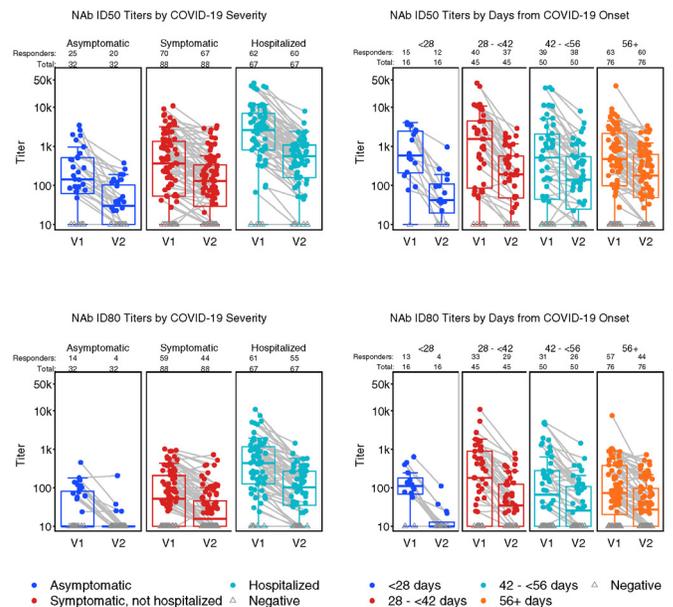
virus infection of 293T/ACE2 cells. Multiple linear regression is applied to define associations between nAb titers and demographic variables, disease severity and duration, and co-morbidities within and across US and Peruvian cohorts over time.

**Results:**

The mean age is 48 years; 49% were assigned female sex at birth, 51% male; 54% are Latinx; 50% identified as Other race, 34% White, 11% Black, 4% Asian. The mean days from SARS-CoV-2 diagnosis to enrollment was 52. NAb titers were higher in participants with a history of severe illness (p<0.001) and peaked 28-42 days post-diagnosis. ID50 (ID80) nAb titers >20 were detected at enrollment in 66% (46%) of asymptomatic, 86% (74%) of symptomatic and 95% (92%) of hospitalized individuals. Median ID50 (ID80) titers at enrollment among asymptomatic, symptomatic and hospitalized individuals were 107 (10), 482 (59) and 1,953 (366), respectively. Two months post-enrollment, median ID50 (ID80) titers among asymptomatic, symptomatic and hospitalized individuals declined to 30 (10), 130 (16) and 564 (103), respectively. Diabetes (p=0.011), age >55yo (p<0.001), male sex (p=0.003) and BMI ≥30 (p=0.021) were associated with higher ID80 titers. Hypertension was associated with lower ID50 titers (p=0.005).

**Conclusion:**

NAb titers after SARS-CoV-2 infection correlate with illness severity and underlying co-morbidities, and peak approximately one month post-diagnosis. Large, diverse, well-characterized cohorts of convalescent individuals facilitate development of standardized laboratory methods and reagents to measure immune responses and provide standardized values to benchmark SARS-CoV-2 vaccine-elicited responses.



**257 SARS-CoV-2 NEUTRALIZING-ANTIBODY RESPONSES IN CONVALESCENT INDIVIDUALS IN US AND PERU**

Shelly Karuna<sup>1</sup>, Sue Li<sup>1</sup>, Shannon Grant<sup>1</sup>, April Randhawa<sup>1</sup>, Meg Trahey<sup>1</sup>, Jen Hanke<sup>1</sup>, Lisa Sanders<sup>1</sup>, Robert De La Grecca<sup>2</sup>, Carissa Karg<sup>1</sup>, Laura Polakowski<sup>3</sup>, John Hural<sup>1</sup>, Jessica Andriesen<sup>1</sup>, Lawrence Corey<sup>1</sup>, David Montefiori<sup>4</sup>, for the HVTN 405/HPTN 1901 Study Team

<sup>1</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Lima, Peru, <sup>3</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, <sup>4</sup>Duke University Medical Center, Department of Surgery, Durham, NC, USA

**Background:**

SARS-CoV-2 has claimed over a million lives and remains a global threat. Understanding immune responses to infection and developing validated laboratory assays to measure them is critical to the rapid development, assessment and implementation of effective interventions. Our development of a validated pseudovirus neutralization assay and characterization of neutralizing antibody (nAb) profiles in a diverse post-SARS-CoV-2 cohort can inform preventative and therapeutic efforts, including vaccine and monoclonal antibody development and deployment.

**Methods:**

This analysis comprises an observational cohort of n=330 adults in the US (n=168) and Peru (n=162), convalescing from SARS-CoV-2 infection and stratified by age, asymptomatic or symptomatic infection, and hospitalization. NAb titers are measured in serum by SARS-CoV-2.D614G Spike-pseudotyped

**258 PERFORMANCE AND DYNAMIC CHANGE IN SARS-CoV-2 ANTIBODY RESPONSES**

Grace Kenny<sup>1</sup>, Willard Tinago<sup>1</sup>, Alejandro Garcia-Leon<sup>1</sup>, Kathleen McCann<sup>1</sup>, Pdraig McGettrick<sup>1</sup>, Sandra Green<sup>1</sup>, Rosanna Inzitari<sup>1</sup>, Aoife G. Cotter<sup>1</sup>, Eoin Feeney<sup>1</sup>, Stefano Savinelli<sup>1</sup>, Peter Doran<sup>1</sup>, Patrick Mallon<sup>1</sup>

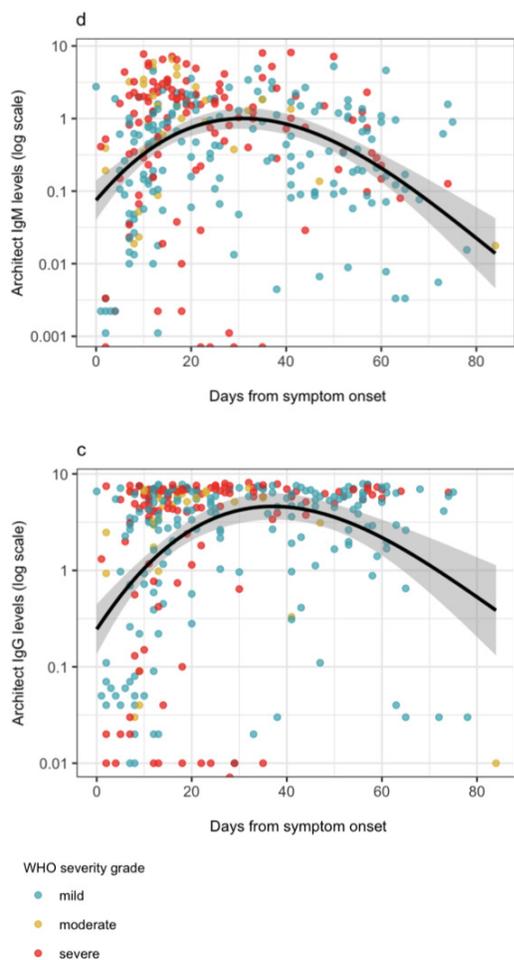
<sup>1</sup>University College Dublin, Dublin, Ireland

**Background:** Although reports suggest that most individuals with COVID-19 infection develop detectable antibodies post infection, the kinetics, durability, and relative differences between IgM and IgG responses remain poorly understood beyond the first few weeks after symptom onset.

**Methods:** Within a large, well-phenotyped, diverse, prospective cohort of subjects with and without SARS-CoV-2 PCR-confirmed infection and historical controls derived from cohorts with high prevalence of viral coinfections and samples taken during prior flu seasons, we measured SARS-CoV-2 serological responses (both IgG and IgM) using three commercially available assays. We calculated sensitivity and specificity, relationship with disease severity and mapped the kinetics of antibody seropositivity and antibody levels over time using generalised additive models.

**Results:** We analysed 1,001 samples (327 confirmed SARS-CoV-2, of whom 30% developed severe disease) from 752 subjects spanning a period of 90 days from symptom onset. Overall sensitivity was lower (44.1–47.1%) early (<10 days) after symptom onset but increased to >80% after 10 days. IgM positivity increased earlier than IgG-targeted assay but positivity peaked between day 32 and 38 post onset of symptoms and declined thereafter, a dynamic that was confirmed when antibody levels were analysed and was more rapid with IgM. Early (<10 days) IgM but not IgG levels were significantly higher in those who subsequently developed severe disease (signal / cut-off 4.20 (0.75–17.93) versus 1.07 (0.21–5.46),  $P=0.048$ ).

**Conclusion:** This study suggests that post-infectious antibody responses in those with confirmed COVID-19 infection begin to decline relatively early post infection and suggests a potential role for higher IgM levels early in infection predicting subsequent disease severity.



## 259 STABLE NEUTRALIZING-ANTIBODY LEVELS 6 MONTHS AFTER MILD AND SEVERE COVID-19 EPISODE

**Edwards Pradenas**<sup>1</sup>, Benjamin Trinité<sup>1</sup>, Victor Urrea<sup>1</sup>, Silvia Marfil<sup>1</sup>, Carlos Ávila-Nieto<sup>1</sup>, María Luisa Rodríguez De La Concepción<sup>1</sup>, Ferran Tarrés-Freixas<sup>1</sup>, Nuria Izquierdo-Useros<sup>1</sup>, Roger Paredes<sup>1</sup>, Lourdes Mateu<sup>2</sup>, Anna Chamorro<sup>2</sup>, Marta Massanella<sup>1</sup>, Jorge Carrillo<sup>1</sup>, Bonaventura Clotet<sup>1</sup>, Julià Blanco<sup>1</sup>  
<sup>1</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>2</sup>Fundació Lluita Contra la Sida, Badalona, Spain

**Background:** One of the fundamental pillars of SARS-CoV-2 pandemic control and vaccine development is understanding mid- and long-term immunity. Early humoral response has been extensively studied, however data on what recovered individuals are still scarce and the most recent studies are based on few time points over time, which limits the comprehension of the longitudinal pattern of the potential changes. In this study we have evaluated the neutralizing activity and IgG antibody titer against SARS-CoV-2 in mild/asymptomatic and hospitalized COVID-19 individuals, over a 6-month period.

**Methods:** We have evaluated the kinetics of the humoral immune response in 210 individuals infected by SARS-CoV-2 covering the first and second waves of COVID-19 outbreak in Catalonia (Spain). IgG antibody titer was evaluated with an in-house sandwich ELISA against the S2 subunit, the binding domain receptor (RBD) and the nucleoprotein (NP) and the neutralizing activity was evaluated by a neutralization assay with HIV reporter pseudoviruses expressing SARS-CoV-2 S protein. Statistical analyses were carried out using mixed-effects non-linear and linear models.

**Results:** Most study participants developed a neutralizing humoral response against SARS-CoV-2, however the maximum neutralization titer was 10-fold lower in mild/asymptomatic individuals compared to those with a more severe illness. We observed a slow and progressive decay of neutralizing activity in individuals with mild or asymptomatic disease throughout the 6-month period. In hospitalized individuals, half maximal neutralization activity was achieved on day 10 and showed an initial rapid decline that significantly slowed and remained nearly flat after day 80. Despite this, activity at six months remained higher in hospitalized individuals compared to mild symptomatic participants. On the other hand, we observed that IgG antibody titers against S2, RBD and NP had a more marked fall without showing differences in the decay pattern between individuals with different degree of severity of the disease.

**Conclusion:** Our data suggest that the neutralizing activity remains relatively stable for more than 6 months despite the decline in IgG antibodies, suggesting that the quality of immune response evolves and allows maintaining the neutralizing activity despite the decay in antibody titers. Our results provide a more detailed picture of the behavior of the natural humoral immune response over time that complements the current evidence on mid-term immunity.

## 260 PERSISTENCE OF SARS-CoV-2 –SPECIFIC AB RESPONSE IN HIV+ INDIVIDUALS ON ART

**Suresh Pallikkuth**<sup>1</sup>, Mark Sharkey<sup>1</sup>, Laura Beauchamps<sup>1</sup>, Patricia Raccamarich<sup>1</sup>, Claudia Uribe<sup>1</sup>, Ana Salazar<sup>1</sup>, Maria Pallin<sup>1</sup>, Elizabeth Varghese<sup>1</sup>, Maragret E. Roach<sup>1</sup>, Alejandro Mantero<sup>1</sup>, Savita G. Pahwa<sup>1</sup>, Deborah Jones Weiss<sup>1</sup>, Maria L. Alcaide<sup>1</sup>

<sup>1</sup>University of Miami, Miami, FL, USA

**Background:** Immune dysfunction characterized by lower antibody (Ab) response to infection or vaccination has been well described among People Living with HIV (PLWH), but due to the novelty of the SARS-CoV-2 virus has not been evaluated among PLWH coinfecting with SARS-CoV-2. This study compared the magnitude and longevity of Ab response to SARS-CoV-2 in a group of HIV+ and HIV- individuals infected with SARS-CoV-2

**Methods:** 17 HIV+ COVID+ and 19 HIV- COVID+ participants were recruited from the community as part of the ACTION study and followed longitudinally at day 14, 1 month and 3 months. HIV+ were on effective ART (plasma viral load <500 copies/ml). SARS-CoV-2 infection was confirmed by SARS-COV2 DNA PCR and rapid antibody test. All participants had mild/moderate COVID-19 without hospitalization. Antibody responses (IgG and IgM) were measured using an indirect in house developed ELISA using spike RBD antigen (courtesy, Scott Boyd, Stanford University) and the data are expressed as relative Ab units based on the positive control standard.

**Results:** The median age of HIV+ participants was 55 (26–63) with 23.5% (4/17) females. The median age for HIV- was 38 (27–78) with 57.8% (11/19) females. Time from COVID-19 diagnosis was 26 days for HIV+ and 21 for HIV-. Mean CD4 count for the HIV+ participants was  $859.5 \pm 287.2$  cells/ $\mu$ l. Longitudinal analysis did not show a significant reduction in Ab response at 3 months in either HIV+ or HIV- groups. Levels of SARS-CoV-2 RBD specific IgM and IgG responses did not differ significantly between HIV+ and HIV- at any timepoint although there was a trend of lower IgM and IgG responses at 3 months in both groups compared to entry levels. Age was correlated with IgG response at day 14 ( $r=0.6$ ,  $p=0.02$ ), 1 month ( $r=0.6$ ,  $p=0.014$ ) and 3 month ( $r=0.87$ ,  $p=0.0008$ ) in HIV+ and weakly correlated at day 14 ( $r=0.46$ ,  $p=0.04$ ) in HIV-. Absolute CD4 count was not correlated with IgM and IgG responses in HIV+.

**Conclusion:** The magnitude and persistence of Ab response to SARS-CoV-2 infection in the 3–4 months post-infection does not differ by HIV status. Although extended longitudinal follow-ups are required to gain insights about the longevity of Ab responses in HIV+ individuals, results suggest that immune protection and vaccine responses may not differ by HIV status.

## 261 BINDING SIGNATURES AND CROSS-REACTIVITY IN THE SARS-CoV-2 IMMUNE RESPONSE



**Caitlin Stoddard**<sup>1</sup>, Jared Galloway<sup>1</sup>, Helen Y. Chu<sup>2</sup>, Mackenzie M. Shipley<sup>1</sup>, Kevin Sung<sup>1</sup>, Hannah L. Itell<sup>1</sup>, Caitlin R. Wolf<sup>2</sup>, Jennifer K. Logue<sup>2</sup>, Ariana Magedson<sup>2</sup>, Meghan Garrett<sup>1</sup>, Katharine H. Crawford<sup>1</sup>, Uri Laserson<sup>3</sup>, Frederick Matsen IV<sup>1</sup>, Julie Overbaugh<sup>1</sup>

<sup>1</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA

**Background:** Mounting evidence indicates that antibodies generated during SARS-CoV-2 infection are correlates of protection. Antibodies targeting Spike (S) on the viral surface have been shown to neutralize the virus. However, the full repertoire of neutralizing and non-neutralizing antibodies against SARS-CoV-2, as well as cross-reactivity between SARS-CoV-2 and other circulating (CoVs), remains unclear. We sought to profile the complete repertoire of linear CoV epitopes targeted by the humoral immune response in patients with and without COVID-19 from Seattle, WA.

**Methods:** To map the linear epitope profiles in patients, we developed a comprehensive pan-CoV phage display library composed of 39 amino acid peptides covering the complete genomes of SARS-CoV-2 and the six other CoVs known to infect humans. Using samples from patients with confirmed COVID-19 and with no known SARS-CoV-2 exposure, we immunoprecipitated antibodies against CoV peptides, deep sequenced the co-immunoprecipitated phage, and applied a customized computational pipeline to define SARS-CoV-2 and cross-reactive epitopes.

**Results:** The dominant immune responses to SARS-CoV-2 were targeted to regions spanning S, Nucleocapsid (N), and ORF1ab. We identified 17 epitopes within S that were present in two or more individuals, spanning both the S1 and S2 subunits, with some detected in > 75% of individuals. The most commonly mapped S epitope (S<sub>1</sub> residues 1121-1159) was a region just upstream of the second heptad repeat. We identified nine epitopes within N that were reactive in at least two individuals, four of which were present in at least 35% of patients. The two most prominent N epitopes were derived from the RNA binding domain (N residues 141-179 and 161-199). Epitopes isolated from ORF1ab were the most variable across patients. Of the 46 unique ORF1ab epitopes we identified, only five were present in two or more individuals, suggesting that ORF1ab responses are individual-specific. We also found a high degree of variation in the total number of epitopes targeted by individuals (ranging from 2 to 25). Finally, we identified four unique cross-reactive sequences that were bound by antibodies in SARS-CoV-2 unexposed individuals.

**Conclusion:** Our study comprehensively defined the linear epitope profiles of a population of COVID-19 and SARS-CoV-2 unexposed patients. Epitope maps and functional characterization of SARS-CoV-2 antibodies will be critical for the development of a broad repertoire of COVID-19 treatments and vaccine strategies.

## 262 CHARACTERIZATION OF SARS-CoV-2-SPECIFIC RESPONSES IN PEOPLE LIVING WITH HIV



**Aljawharah S. Alrubayyi**<sup>1</sup>, Ester Gea-Mallorqui<sup>1</sup>, Emma Touizer<sup>2</sup>, Dan HameiriBowen<sup>1</sup>, Jakub Kopycinski<sup>1</sup>, Bethany Charlton<sup>1</sup>, Natasha Fisher-Pearson<sup>1</sup>, Pierre Pellegrino<sup>3</sup>, Laura Waters<sup>3</sup>, Burns Fiona<sup>2</sup>, Sabine Kinloch-de Loes<sup>4</sup>, Lucy Dorrell<sup>1</sup>, Sarah Rowland-Jones<sup>1</sup>, Laura E. McCoy<sup>2</sup>, Dimitra Peppas<sup>1</sup>

<sup>1</sup>University of Oxford, Oxford, UK, <sup>2</sup>University College London, London, UK, <sup>3</sup>Mortimer Market Centre, London, UK, <sup>4</sup>Royal Free Hospital, London, UK

**Background:** There is an urgent need to understand the nature of immune responses mounted against SARS-CoV-2, in order to better inform risk-mitigation and vaccine strategies for people living with HIV (PLWH). Although not all PLWH are considered immunosuppressed, residual cellular immunodeficiency could influence COVID-19 disease severity and the evolution and durability of protective immunity. Information on the breadth, magnitude and longevity of SARS-CoV-2 specific responses in PLWH recovering from COVID-19 disease is currently lacking. In this study, we performed an integrated cross-sectional analysis of different branches of adaptive immunity to SARS-CoV-2 in PLWH and HIV negative donors in the convalescent phase of predominately mild COVID-19 disease.

**Methods:** A total of n=47 HIV positive, controlled on ART, and n=35 HIV negative subjects were recruited at a median of 158 and 146 days post symptom onset respectively. SARS-CoV-2 antibodies against Spike (S1) and Nucleoprotein (N) were measured in serum by a Semiquantitative ELISA. A serum neutralisation assay with pseudotyped SARS-CoV-2 was performed to

calculate the 50% inhibitory serum dilution (ID50). SARS-CoV-2 specific memory T cell responses were determined by IFN- $\gamma$  ELISpot and intracellular cytokine production assays using peptide pools against SARS-CoV-2 structural and accessory proteins (Spike, Membrane, Nucleocapsid, Envelope, and ORF3a,6,7,8).

**Results:** The majority of PLWH had detectable SARS-CoV-2 S- and N-specific antibodies with neutralizing activity at levels comparable to HIV negative subjects ( $p=0.5753$ ). Although, the overall magnitude of SARS-CoV-2 specific T cell responses measured by ELISpot was not significantly different between the groups ( $p=0.4642$ ), this correlated with the size of the naïve CD4 T cell pool ( $r=0.5518$ ,  $p=0.0143$ ) and the CD4:CD8 ratio in PLWH ( $r=0.3820$ ,  $p=0.037$ ). In both groups, SARS-CoV-2 specific CD4 T cells were more abundant compared to CD8 T cells (HIV-  $p=0.002$ , HIV+  $p=0.0019$ ). Both humoral and cellular responses were detected between 5-7 months post infection, providing evidence of medium-term durability of responses irrespective of HIV serostatus.

**Conclusion:** The majority of PLWH mount a functional adaptive immune response to SARS-CoV-2. Incomplete immune reconstitution on ART and persistent alterations in the T cell compartment could, however, impact the development of protective immunity to SARS-CoV-2. These findings have implications for the risk stratification and management of PLWH.

263



## ESCAPE OF SARS-CoV-2 501Y.V2 VARIANTS FROM NEUTRALIZATION BY CONVALESCENT PLASMA

**Sandile Cele**<sup>1</sup>, Inbal Gazy<sup>2</sup>, Laurelle Jackson<sup>1</sup>, Shi-Hsia Hwa<sup>1</sup>, Houriyah Tegally<sup>3</sup>, Farina Karim<sup>1</sup>, Gila Lustig<sup>4</sup>, Alejandro Balazs<sup>5</sup>, Willem A. Hanekom<sup>1</sup>, Bernadette Gosnell<sup>6</sup>, Mahomed-Yunus Moosa<sup>6</sup>, Richard Lessells<sup>3</sup>, Tulio de Oliveira<sup>3</sup>, Alex Sigal<sup>1</sup>

<sup>1</sup>Africa Health Research Institute, Mtubatuba, South Africa, <sup>2</sup>Hebrew University of Jerusalem, Jerusalem, Israel, <sup>3</sup>KwaZulu-Natal Research Innovation and Sequencing Platform, Durban, South Africa, <sup>4</sup>Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, <sup>5</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>6</sup>University of KwaZulu-Natal, Durban, South Africa

**Background:** New SARS-CoV-2 variants with mutations in the spike glycoprotein have arisen independently at multiple locations and may have functional significance. The combination of mutations in the 501Y.V2 variant first detected in South Africa include the N501Y, K417N, and E484K mutations in the receptor binding domain (RBD) as well as mutations in the N-terminal domain (NTD). Here we address whether the 501Y.V2 variant could escape the neutralizing antibody response elicited by natural infection with earlier variants.

**Methods:** We were the first to outgrow two variants of 501Y.V2 from South Africa, designated 501Y.V2.HV001 and 501Y.V2.HVdF002. We examined the neutralizing effect of convalescent plasma collected from adults hospitalized with COVID-19 using a microneutralization assay with live (authentic) virus. Whole genome sequencing of the infecting virus of the plasma donors confirmed the absence of the spike mutations which characterize 501Y.V2. We infected with 501Y.V2.HV001 and 501Y.V2.HVdF002 and compared plasma neutralization to first wave virus which contained the D614G mutation but no RBD or NTD mutations.

**Results:** We observed a reduction in antibody activity ranging from 6-fold to knockout for the 501Y.V2 (B.1.351) relative to the B.1.1 variant derived from the first wave of the pandemic in South Africa.

**Conclusion:** This observation indicates that 501Y.V2 may escape the neutralizing antibody response elicited by prior natural infection. It raises a concern of potential reduced protection against re-infection and by vaccines designed to target the spike protein of earlier SARS-CoV-2 variants.

264

## HIGH-RESOLUTION MAPPING OF T-CELL IMMUNITY TO THE ENTIRE SARS-CoV-2 PROTEOME

**Athina Kilpeläinen**<sup>1</sup>, Luis Romero<sup>1</sup>, Oscar Blanch-Lombarte<sup>1</sup>, Bibiana Quirant<sup>2</sup>, Esther Jiménez-Moyano<sup>1</sup>, Dan Ouchi<sup>1</sup>, Aleix Pujol-Gimeno<sup>2</sup>, Noemi Lamonja-Vicente<sup>2</sup>, Eva Martínez-Caceres<sup>3</sup>, Concepción Violán-Fors<sup>4</sup>, Pere Torán-Monserrat<sup>4</sup>, Bonaventura Clotet<sup>1</sup>, Christian Brander<sup>5</sup>, Alex Olvera<sup>1</sup>, Julia G. Prado<sup>1</sup>

<sup>1</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>2</sup>Germans Trias i Pujol Research Institute, Badalona, Spain, <sup>3</sup>Germans Trias i Pujol Research Institute, Immunology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, <sup>4</sup>Immunology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, <sup>5</sup>IrsiCaixa, Institutió Catalana de Recerca i Estudis Avançats, Barcelona, Spain

**Background:** Since the discovery of SARS-CoV-2, researchers have put major efforts towards the understanding of virus-specific cellular immunity. However,

the identification of epitope- and protein specific T-cell responses is limited to bioinformatic approaches, use of total viral proteins or peptide mega pools. To overcome these current limitations, we performed a high-resolution mapping using IFN- $\gamma$  ELISpot and peptide sets covering the entire CoV-2 proteome.

**Methods:** We synthesized a 15-mer peptide library of 2790 peptides (11 amino acid overlap) covering a CoV-2cons proteome sequence based on 1700 sequences. We designed a mega matrix of consecutive and non-consecutive peptide pools with 20 to 35 peptides per pool. We assessed T-cell responses in cryopreserved PBMCs from IgG+ SARS-CoV-2 infected individuals (N=13), who recovered from mild/moderate infection, 90-190 Days from off-set symptoms. Also, we expanded PBMCs in the presence of anti-CD3 and IL-2 during 3 weeks and performed a comparative ELISpot using total and expanded PBMCs.

**Results:** Frequencies of T-cell responses from positive peptide pools revealed 40% of responses targeting S2, 20% against S1, 10% against M, and 6% against nsp3 and NP, respectively. The strongest responses were targeting S2 and S1 (median values of 540 and 240 IFN- $\gamma$  SFC/10<sup>6</sup>, respectively), followed by nsp3, NP and M. We observed a median of 13 deconvoluted reactive peptides across the entire proteome per tested individual. The breadth of responses ranged from 1-8 targeted proteins with a median of 2. In addition, we mapped responses in subproteins 3C-LP, nsp6, nsp10 (Orf1ab), and alternative reading frames. We also identified responses to peptide sequences conserved across pan-coronavirus strains Orf1b (n=2), S (n=1) and M (n=1). Following expansion, we observed a loss of CD4+ T-cells in cultured cells and altered peptide-recognition profiles characterized by a loss of S2 and an increase of nsp3 responses.

**Conclusion:** We characterize protein hierarchy in terms of breadth and magnitude by high-resolution mapping of T-cell responses against the entire CoV-2 proteome. The most frequently targeted and immunogenic regions were S2 and S1. We identify responses to small proteins, alternative reading frames and conserved regions across coronaviruses. This data brings new insight into the complexity of CoV-2 T-cell responses and crucial information for vaccine design.

## 265 SARS-CoV-2 NON-SEROCONVERTORS PRESENT T-CELL RESPONSES WITH DECREASED ACTIVATION

**Athina Kilpeläinen**<sup>1</sup>, Esther Jiménez-Moyano<sup>1</sup>, Ruth Peña<sup>1</sup>, Oscar Blanch-Lombarte<sup>1</sup>, Anna Chamorro<sup>2</sup>, Eva Martínez-Caceres<sup>3</sup>, Ignacio Blanco<sup>4</sup>, Jorge Carrillo<sup>1</sup>, Julià Blanco<sup>1</sup>, Christian Brander<sup>5</sup>, Lourdes Mateu<sup>6</sup>, Roger Paredes<sup>1</sup>, Bonaventura Clotet<sup>1</sup>, Marta Massanella<sup>1</sup>, Julia G. Prado<sup>1</sup>

<sup>1</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>2</sup>Fundació Lluita Contra la Sida, Badalona, Spain, <sup>3</sup>Immunology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, <sup>4</sup>Hospital Universitari Germans Trias i Pujol, Institut d'Investigació Germans Trias i Pujol, Barcelona, Spain, <sup>5</sup>IrsiCaixa, Institut Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain, <sup>6</sup>Infectious Diseases Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

**Background:** Many immune studies of SARS-CoV-2 (CoV-2) infection have focused on the generation of virus-specific as a means of protection. However, a small group of CoV-2 infected individuals called Non-seroconverters (NSC), do not generate antibodies but experience a mild or moderate disease course. Identifying mechanism of CoV-2 control in NSC may inform the development of novel therapeutics and vaccines approaches.

**Methods:** We identified eleven CoV-2 NSC (3.6%) from the King-cohort study (PI-20-217). NSC were defined by a positive CoV-2 PCR at the time of diagnosis in the absence of IgG, IgA and IgM in serum and plasma measured by two independent ELISA techniques. For comparison, we identify groups of CoV-2 convalescent (n=15) and low-neutralizers (n=15). We measured T-cell responses to the CoV-2 Spike (S) and Nucleocapsid (NP) recombinant proteins in PBMCs by ELISpot and flow cytometry. We combined T-cell surface and lineage markers together with PD-1, functional (TNF, IFN- $\gamma$ , and IL-2) and activation induced markers (AIM: CD25, CD137 and OX40).

**Results:** We identified CoV-2 specific CD4+ and CD8+ T-cells against the S and the NP in NSC individuals. All NSC responded to S by production of one or more cytokine in either CD4+ or CD8+ T-cells, and 57% responded to NP. Specific-CD8+ T cells against S in NSC were characterized by IFN- $\gamma$ , and TNF production, and we observed higher levels of TNF production as compared to low neutralizers (p=0.02). No differences were found in IFN- $\gamma$ , IL-2 and TNF production in S-specific CD4+ T cells between groups, nor in NP CD8+ or CD4+ T-cell responses. The levels of CD137/OX40 in CD8+ and CD4+ T cells were significantly lower in NSC in response to S (p=0.006, and p=0.012). Also, lower levels of PD-1 were observed in CD8+ T cells in response to NP in NSC (p=0.017).

**Conclusion:** We provide evidence of SARS-CoV2 cellular immunity in NSC individuals despite the absence of humoral neutralizing responses. CD8+ and CD4+ T cells against the S and NP were present in NSC and characterized by TNF production in CD8+ T-cells in responses to S when compared to low neutralizers. Decreased levels of activation markers were observed in NSCs following S and NP stimulation. We propose a protective role of cellular immunity in NSC potentially driven by preexisting cellular responses.

## 266 IMPAIRMENT OF TYPE I/III IFN RESPONSE IN THE UPPER AIRWAYS OF SARS-CoV-2 PATIENTS

**Federica Frasca**<sup>1</sup>, Mirko Scordio<sup>1</sup>, Agnese Viscido<sup>1</sup>, Giuseppe Oliveto<sup>1</sup>, Camilla Bitossi<sup>1</sup>, Carolina Scagnolari<sup>1</sup>

<sup>1</sup>Sapienza University of Rome, Rome, Italy

**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become the most severe public healthcare concern. Interferon (IFN) represents a critical, first-line defense to viral infection and injury as part of innate immunity. Therefore, in order to provide additional insights to the pathogenesis of SARS-CoV-2, we delineated IFN signatures in the upper respiratory tract of 2019-nCoV patients through the investigation of genes encoding type I/III IFNs, IFN-regulatory factor 7 (IRF-7) and IFN stimulated genes (ISGs).

**Methods:** Respiratory samples of 54 patients with symptomatic SARS-CoV-2 infection and 29 negative healthcare workers were collected in our study. Oropharyngeal swabs were divided into two aliquots: one was treated for SARS-CoV-2 detection and one was used to extract total RNA from pellet cells and to analyze gene expression of IFN- $\alpha$ , IFN- $\beta$ , IFN- $\lambda$  1-3, IRF7, ISG15, and ISG56 through RT/Real Time PCR.

**Results:** Overall IFN- $\alpha$ , IFN- $\beta$ , IFN- $\lambda$  1-3, IRF7, and ISGs mRNA levels in oropharyngeal swabs were significantly increased in SARS-CoV-2 infected patients compared to those detected in healthcare workers. SARS-CoV-2 threshold cycle (Ct) values negatively correlated to ISG15, ISG56 and IRF7 mRNAs levels (ISG15 r=-0.3066, p=0.0405; ISG56 r=-0.3672, p=0.0182; IRF7 r=-0.3733, p=0.0192). Interestingly, the subgroup of 6 patients who were supported by invasive mechanical ventilation showed a general decrease in the expression of some IFN genes with a significant lower level of ISG15 and ISG56, compared to the patients who do not required oxygen support and those who received non-invasive ventilation (p<0.05; p<0.05).

**Conclusion:** Our results suggest a differential IFN-I/III signature in the respiratory tract of SARS-CoV-2 patients, depending on development of immunopathology and severe disease. Understanding of the effects of SARS-CoV-2 on the overall innate immune response with the final aim to shed new light on COVID-19 pathogenesis and design a tailored immune-therapy for SARS-CoV-2 infected patients.

## 267 A NOVEL VSV-BASED EBOLA/HIV-1 VACCINE PROVIDES PROTECTION IN MACAQUES FROM SHIV

**Eric J. Arts**<sup>1</sup>, Alice Berger<sup>2</sup>, Jannie Pedersen<sup>2</sup>, Jason J. Knapp<sup>1</sup>, Hiva Azizi<sup>2</sup>, Yue J. Li<sup>2</sup>, Marc-Alexander Lafrance<sup>2</sup>, Florine Scholte<sup>2</sup>, Jamie J. Mann<sup>1</sup>, Amine Kamen<sup>3</sup>, Keith Fowke<sup>4</sup>, Eric A. Cohen<sup>5</sup>, Chil-Yong Kang<sup>1</sup>, Gary Kobinger<sup>2</sup>

<sup>1</sup>Western University, London, Canada, <sup>2</sup>Laval University, Quebec City, Canada, <sup>3</sup>McGill University, Montreal, Canada, <sup>4</sup>University of Manitoba, Winnipeg, Canada, <sup>5</sup>IRCM, Montreal, Canada

**Background:** Over 30 VSV-based vaccine constructs in absence of VSV-G were engineered to contain HIV-1 Env chimeras with or without SIV gag and with or without the Ebola glycoprotein to drive vector propagation. After pre-clinical analyses of production/expression and small animal testing, a subset of 5 vaccine constructs were used to immunize macaques that were later challenge with low dose SHIV.

**Methods:** Codon-optimized HIV-1 ecto/gp140 Env of a subtype A strain with different transmembrane and intracellular tails (TMIC) of the VSV G, Ebola GP, mutated HIV-1, and SIVmac239 Env were cloned into and expressed in VSVdelG vectors. VSVdelG replication was driven either by the functional HIV chimera or by the cis addition of Ebola or Marburg GP. Expression and Env function for entry was tested and VSV vectors were produced for mouse immunizations to measure humoral (binding and neutralizing Abs) and CTL responses. The best candidates were then tested in rabbits and macaque challenge studies.

**Results:** From the 30+ candidates screen, VSVdelG expressing Ebola or Marburg GP along with the A74-gp140/SIV-TMIC displayed the highest level of surface HIV-1 Env expression and robust vector propagation. Details of the three year preclinical screening and small animal testing will be provided in the

presentation. The best candidate, VSVdelG\_A74-gp140/SIV-TM1C\_Ebola-GP was used as the prime followed by a boost with VSVdelG\_SIV-Gag + A74-gp140/SIV-TM1C\_Ebola-GP and then a boost with VSVdelG\_A74-gp140/SIV-TM1C\_Ebola\_GP (Grp1). Only four out of ten animals in this vaccinated Grp1 group were infected by the 7th challenge. Eight of 10 in the control macaques (Grp3) and 10 of 10 alternative vaccine group (Grp3) were infected with SHIV\_SF162-p3 during the 7 low dose challenges.

**Conclusion:** Building on the VSV-Ebola vaccine technology, we engineered an improved VSV-vectored vaccine for HIV prevention. We observed one of the best protections against low dose heterologous SHIV challenges in macaques to date. Analyses on macaque samples suggest that the use of VSV-based HIV Env construct with Gag may be important for protection, especially in boosting CTL response, but its inclusion in the final boost (groups 2 and 3) may promote an activated CD4+ T cell population capable of increasing SHIV infection. These findings suggest an important balance of cell based versus humoral immunity in the use of vaccine constructs in prime/boost strategies for optimal protection.

## 268 DESIGN AND IMMUNOGENICITY OF V3-GLYCAN EPIOTOPE-FOCUSED NANOPARTICLES FOR HIV VACCINES

Christine N. Daniels<sup>1</sup>, Esther Lee<sup>1</sup>, Cindy N. Bowman<sup>1</sup>, Celia LaBranche<sup>1</sup>, Robert Edwards<sup>1</sup>, Brian Watts<sup>1</sup>, M. G. Joyce<sup>2</sup>, David Montefiori<sup>1</sup>, Munir S. Alam<sup>1</sup>, Barton Haynes<sup>1</sup>, Kevin Saunders<sup>1</sup>

<sup>1</sup>Duke Human Vaccine Institute, Durham, NC, USA, <sup>2</sup>Military HIV Research Program, Silver Springs, MD, USA

**Background:** Induction of broadly neutralizing antibodies (bnAbs) that confer protection against diverse strains is a primary goal of HIV-1 vaccine design. In order accomplish this feat, antibodies must target conserved sites on the envelope (Env) surface. The V3-glycan epitope is a well-defined site of vulnerability targeted by a class of antibodies with extreme neutralization potency and breadth. We designed minimal nanoparticle-based immunogens that recapitulate this conserved site to focus the immune response on the V3-glycan epitope. We hypothesize vaccination with minimal immunogens will target and expand subdominant neutralizing antibodies (nAbs) without boosting dominant strain-specific non-nAbs.

**Methods:** V3-glycan epitope nanoparticles were produced in Freestyle293 cells and purified by 2G12 affinity chromatography. Formation of nanoparticles was determined by negative stain electron microscopy. Immunogen recognition by bnAbs was assessed by ELISA. Immunogenicity studies were performed using female New Zealand white rabbits. Rabbits (n=5 per group) were immunized intramuscularly with either SOSIP or adjuvant at week 0, 4 and 8. Animals received boosts with the V3-glycan epitope nanoparticle at weeks 12 and 22. Serum was collected 2 weeks after each immunization. Serum antibody binding titers were determined by ELISA. Epitope mapping of serum antibodies was assessed by decreases in binding to Env with mutated epitopes. Serum nAbs were determined by the TZM-bl assay using pseudoviruses.

**Results:** We generated ferritin nanoparticles that each display 24 copies of a glycopeptide that mimics the V3-glycan epitope. These nanoparticles are antigenic for V3-glycan bnAbs but not linear V3 antibodies. Binding of the bnAbs was further enhanced by enriching for Man9GlcNAc2 protein glycosylation. Rabbits received three immunizations with a group M consensus stabilized Env SOSIP followed by two boosts with the glycan-V3 ferritin nanoparticles. A single boost elicited antibodies with preferential binding to the glycopeptide versus the aglycone peptide. A second boost increased glycopeptide binding, but also induced V3 peptide-specific antibodies. Boosting sustained titers of SOSIP-specific antibodies for 22 weeks–12 weeks after the final trimer immunization.

**Conclusion:** Glycan-V3 nanoparticle vaccination elicited V3-directed antibodies that were predominantly glycan-dependent. Our results establish a nanoparticle platform by which minimal immunogens can be used to target antibodies to a specific epitope.

## 269 NANOPARTICLE-DCs RESTORE CYTOTOXIC MEMORY-LIKE NK CELLS IN CHRONIC HIV PATIENTS

Ildefonso S. Cerrillo<sup>1</sup>, Marta Calvet-Mirabent<sup>1</sup>, Cristina Delgado<sup>1</sup>, Ignacio De Los Santos<sup>1</sup>, Jesus Sanz<sup>1</sup>, Lucio Jesús F. García-Fraile<sup>1</sup>, María José Buzón<sup>2</sup>, María Ángeles Muñoz-Fernández<sup>3</sup>, Francisco Sanchez<sup>2</sup>, Enrique Martín-Gayo<sup>4</sup>

<sup>1</sup>Hospital Universitario de La Princesa, Madrid, Spain, <sup>2</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, <sup>3</sup>Hospital General Universitario Gregorio Marañón, Madrid, Spain, <sup>4</sup>Universidad Autónoma de Madrid, Madrid, Spain

**Background:** Cytotoxic CD16+ Natural Killer (NK) cells become dysfunctional in HIV-1 chronically infected individuals even after antiretroviral therapy initiation, preventing effective elimination of HIV-1 infected cells. Previous studies suggest that activated dendritic cells (DC) stimulate NK and might be useful for therapeutic purposes. However, DCs from chronic HIV-1 patients can also be unresponsive to adjuvant stimulation. Thus, new approaches are needed to maximize DC-NK crosstalk in chronic HIV-1 patients. Here, we evaluated the efficacy of DC conditioned with nanoparticles containing Poly I:C preserving cytotoxic function of CD16+ NK cells from HIV-chronic patients.

**Methods:** Monocyte-Derived Dendritic Cells (MDDCs) were derived from peripheral blood monocytes from aviremic treated chronic HIV-1 patients or from healthy donors in the presence of GM-CSF and IL4 for 5 days. MDDCs were exposed to either soluble or nanoparticle-loaded Poly I:C (PI:C) and expression of inflammatory cytokines and NK cell receptor ligands was determined after 24h by multicolor flow cytometry. Unstimulated or nanoparticle-treated MDDCs were co-cultured with autologous NK cells and expression of CD107a, NKG2C and CD57 was also determined by FACS. Natural cytotoxic function of NK cells was assessed by coculture with the target cell line K562-GFP. Finally, NK cells from treated HIV patients were incubated with autologous CD4+ T cells in the presence of IL-2, Raltegravir and Romidepsin. Proportions of HIV-1 p24+ CD4+T cells detected after treatment with NK cells was evaluated after 24h by FACS.

**Results:** MDDC treated with PI:C-nanoparticles express higher levels of IL-12 and IFN- $\beta$  (p=0.03; p=0.03) and MICAB, ULBP1 ligands for NK receptors, in contrast to MDDC treated with soluble PI:C. MDDCs conditioned with PI:C-nanoparticles were capable of inducing higher frequencies of cytotoxic CD107a+ CD16+ NK cells (p=0.01) characterized by effective natural cytotoxic function (p=0.01). Importantly, MDDC from chronic HIV-1 patients also express higher levels of activating NK receptor ligands (p=0.0001), increased proportions of memory-like NKG2C+ CD57+ CD16+ NK cells (p=0.03) and induced a more effective reduction of autologous HIV p24+ expressing CD4+ T cells (p=0.01) after PI:C-nanoparticle treatment.

**Conclusion:** Conditioning of DC with PI:C-nanoparticles is a promising tool to restore natural cytotoxic function of CD16+ NK cells from chronic ART-treated HIV-1 patients and more efficiently targeting HIV-1 infected CD4+ T cells.

## 270 AAV-EXPRESSED ANTI-HIV BIOLOGICS BLOCK ORAL SHIV ACQUISITION IN INFANT RHESUS MONKEYS

Amir Ardehsir<sup>1</sup>, Koen K. Van Rompay<sup>1</sup>, Sebastian P. Fuchs<sup>2</sup>, Matthew R. Gardner<sup>3</sup>, Rubens Tavora<sup>4</sup>, Ronald C. Desrosiers<sup>2</sup>, Michael Farzan<sup>4</sup>, Mauricio A. Martins<sup>4</sup>

<sup>1</sup>University of California Davis, Davis, CA, USA, <sup>2</sup>University of Miami, Miami, FL, USA, <sup>3</sup>Emory University, Atlanta, GA, USA, <sup>4</sup>Scripps Research Florida, Jupiter, FL, USA

**Background:** Antiretroviral therapy has been highly effective in limiting mother-to-child transmission of HIV but has suffered from problems related to accessibility and compliance. Given these issues, we have begun studies in infant rhesus macaques (RMs) to assess the potential of long-term delivery of anti-HIV biologics using adeno-associated virus (AAV) as a vector for the prevention of postpartum HIV transmission.

**Methods:** Nine newborn RMs were evenly divided among 3 groups depending on which AAV treatment they received. Group 1 was treated intramuscularly (IM) with an AAV1 vector encoding the immunoadhesin eCD4-Ig. Group 2 was dosed with AAV8/eCD4-Ig intravenously at birth, followed by an IM dose of AAV1/eCD4-Ig four weeks later. Group 3 was inoculated IM with an AAV8 vector encoding the broadly neutralizing antibody 3BNC117. Beginning at week 30, the infants in Groups 1-3, together with 6 age-matched control RMs, were subjected to weekly oral challenges with escalating doses of SHIV-AD8. Serum levels of eCD4-Ig, 3BNC117, and anti-drug antibodies (ADAs) were measured by ELISA. Plasma viral loads were measured by real-time PCR.

**Results:** All AAV inoculations were well tolerated. All RMs in Groups 1 and 2 developed persistent serum levels of eCD4-Ig in the 12-70  $\mu$ g/ml range. Although one animal in each group mounted ADAs, these responses did not abrogate eCD4-Ig expression. Of the three RMs in Group 3, two developed

persistent levels of 3BNC117 in the 48–79 µg/ml range. The third animal mounted a robust ADA response that drove its 3BNC117 levels to below detection limits. After 12 oral exposures to SHIV-AD8, all control infants became infected, compared to one RM in Groups 1–3 ( $P = 0.0004$ ). Importantly, the protected AAV-treated RMs have maintained persistent expression of eCD4-Ig or 3BNC117 for >21 months post AAV inoculation.

**Conclusion:** Neonatal delivery of AAV vectors encoding anti-HIV biologics can block oral SHIV acquisition in infant RMs. Given the potential of this strategy to generate broad, potent, and durable anti-HIV immunity after a single dose, studies aimed at evaluating the safety and antiviral efficacy of AAV-vectored HIV immunotherapy in human infants seem warranted.

## 271 PROTECTION FROM SHIV INFECTION IN IMMUNE-COMPLEX VACCINATED RHESUS MACAQUES



**Qingbo Liu**<sup>1</sup>, Peng Zhang<sup>1</sup>, Kristin L. Boswell<sup>2</sup>, Amy T. Noe<sup>2</sup>, Claire Deleage<sup>3</sup>, Huiyi Miao<sup>1</sup>, Denise A. Rogers<sup>1</sup>, Hana Schmeisser<sup>1</sup>, Richard L. Herbert<sup>4</sup>, Joanna Swerzek<sup>4</sup>, Kristen N. Kaiser<sup>4</sup>, Kathryn E. Foulds<sup>2</sup>, Richard A. Koup<sup>2</sup>, Anthony S. Fauci<sup>1</sup>, Paolo Lusso<sup>1</sup>

<sup>1</sup>Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, <sup>2</sup>Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, <sup>3</sup>Leidos Biomedical Research, Inc, Frederick National Laboratory for Cancer Research, Frederick, MD, USA, <sup>4</sup>Experimental Primate Virology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Poolesville, MD, USA

**Background:** Immune complex (IC) vaccines have been reported to be more efficient in presenting antigens to the immune system and to promote cross-presentation of exogenous antigens on class-I MHC. Here, we tested the immunogenicity and efficacy of a virus-like particle (VLP)-based IC vaccine in a non-human primate model.

**Methods:** VLPs were produced by transfecting an SIV backbone into an HEK293 clone stably expressing HIV-1 Env (WITO). A4b7+ VLPs were produced by co-transfection of a4 and b7 subunits. Five groups of rhesus macaques ( $N = 5$ ) were vaccinated by 6 sequential s.c. inoculations of pre-formed ICs over a period of 4 months, with an additional group serving as naïve controls. ICs were formed with either a bNAb (VRC26), or a primatized anti-a4b7 antibody (ACT-1, wild-type or Fc-defective), with two control groups receiving a4b7-negative VLPs mixed with ACT-1 or an irrelevant IgG. After vaccination, all animals were challenged by 12 repeated low-dose intrarectal inoculations of a non-pathogenic tier-1b SHIV, BaL, followed 3 months later by rechallenge with a pathogenic tier-2 SHIV, AD8. Viral Load and antiviral T-cell responses were monitored. ELISA and TZM-bl assay were used to test Env-specific antibody production.

**Results:** All animals in the control group were rapidly infected by SHIV BaL reaching high levels of viremia, while the bNAb-IC group was partially protected with two animals remaining uninfected and the other three showing marked reductions of peak viremia. Four additional animals in three other vaccine groups remained uninfected; however, viremia in those infected animals reached regularly high levels. SHIV BaL replication was rapidly controlled in all infected animals. Following rechallenge with SHIV AD8, all animals previously uninfected with BaL were rapidly infected with AD8 reaching high levels of viremia. In contrast, half of those previously infected with BaL were completely protected from AD8, while the remaining showed significantly reduced and delayed viremia. Protection from AD8 superinfection was associated with robust Gag- and Env-specific T-cell responses. Antibody-mediated CD8a depletion caused a rapid viral rebound in all animals.

**Conclusion:** An IC vaccine with bNAbs provided partial protection against a non-pathogenic SHIV (BaL) in macaques. However, previous exposure to BaL conferred a strong protection from a pathogenic tier-2 heterologous strain (AD8). Virus-specific T-cell responses were correlated with protection, with a key role played by CD8 T cells.

272



## DUAL-ANTIGEN COVID-19 VACCINATION WITH ORAL BOOST PROTECTS NHP FROM VIRAL CHALLENGE

**Elizabeth R. Gabitzsch**<sup>1</sup>, Jeffrey T. Safrit<sup>2</sup>, Mohit Verma<sup>1</sup>, Adrian Rice<sup>1</sup>, Peter Sieling<sup>1</sup>, Helty Adisetiyo<sup>1</sup>, Annie Shin<sup>1</sup>, Raymond Wong<sup>1</sup>, Victor Peykov<sup>1</sup>, Hermes Garban<sup>1</sup>, Daniel C. Sanford<sup>3</sup>, Patricia R. Spilman<sup>1</sup>, Shahrooz Rabizadeh<sup>1</sup>, Kayvan Niazi<sup>1</sup>, Patrick Soon-Shiong<sup>1</sup>

<sup>1</sup>ImmunityBio, Inc, Culver City, CA, USA, <sup>2</sup>NantKwest, Inc, Culver City, CA, USA,

<sup>3</sup>Battelle Biomedical Research Center, Columbus, OH, USA

**Background:** To address the need for an efficacious COVID-19 vaccine suitable for world-wide distribution, we have developed a dual-antigen vaccine incorporating genes for a modified SARS-CoV-2 spike protein (S-Fusion) and the viral nucleocapsid protein (N) with an Enhanced T-cell Stimulation Domain (N-ETSD) with the potential to increase MHC class I/II responses. The adenovirus serotype 5 platform used, hAd5 [E1-, E2b-, E3-] can be delivered in an oral formulation that overcomes cold-chain limitations. The hAd5 S-Fusion + N-ETSD vaccine was evaluated in rhesus macaques to determine both humoral and cell-mediated responses to vaccination, and protection from subsequent SARS-CoV-2 challenge.

**Methods:** Non-human primates (NHP) received either a subcutaneous (SC) prime and two oral boosts at 2-week intervals, or one SC and one oral boost (each group  $n = 5$ ). There was also a placebo group ( $n = 2$ ). Humoral responses to spike (S) were determined by ELISA and T-cell responses to S and nucleocapsid (N) by ELISpot. Neutralization capability of sera was assessed by a surrogate assay and by a microneutralization assay. After SARS-CoV-2 challenge of  $10e6$  TCID50, genomic RNA (gRNA) and subgenomic RNA (sgRNA) were determined in nasal swab and bronchoalveolar lavage (BAL) samples by RT-qPCR.

**Results:** In response to hAd5 S-Fusion + N-ETSD vaccination, NHP generated SARS-CoV-2-neutralizing anti-spike (S) antibodies and demonstrated T-cell activation by both S and nucleocapsid (N). Both the subcutaneous (SC) prime followed by two oral boosts or an SC and oral boost protected the upper and lower respiratory tracts of non-human primates from high titer SARS-CoV-2 challenge. Notably, inhibition of viral replication began within 24 hours of challenge in both lung and nasal passages, becoming undetectable within 7 days post-challenge. Rapidly enhanced neutralization capability of sera in the two weeks after challenge suggests the presence of memory B cells that were activated by infection.

**Conclusion:** The hAd5 S-Fusion + N-ETSD vaccine, when given as a subcutaneous prime with oral boosts, protects rhesus macaques from subsequent viral challenge. The decrease in subgenomic RNA seen at the first time point for sample collection post-challenge (24 hours) provides evidence that protection was almost immediate. The thermally-stable oral form of the vaccine has the potential to facilitate global distribution of vaccines, especially in developing nations.

273

## DISTINCT TISSUE TOPOLOGY AND CELL PHENOTYPES PREDICT NEUTRALIZATION IN HIV INFECTION

**Eirini Moysi**<sup>1</sup>, Perla Mariana Del Rio Estrada<sup>2</sup>, Gustavo Reyes-Teran<sup>2</sup>, Clarisa Buckner<sup>3</sup>, Alexander J. Chassiakos<sup>1</sup>, Ashish A. Sharma<sup>4</sup>, Sijy O'Dell<sup>1</sup>, Nicole Doria-Rose<sup>1</sup>, Margaret H. Beddall<sup>1</sup>, Susan Moir<sup>3</sup>, Rafick-Pierre Sékaly<sup>4</sup>, John R. Mascola<sup>1</sup>, Richard A. Koup<sup>1</sup>, Constantinos Petrosvas<sup>1</sup>

<sup>1</sup>Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, <sup>2</sup>Centro de Investigación en Enfermedades Infecciosas, Mexico City, Mexico, <sup>3</sup>Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, <sup>4</sup>Department of Pathology, Emory University, Atlanta, GA, USA

**Background:** The induction of broadly neutralizing antibodies (bNAbs) is a major goal of HIV vaccine efforts. In chronic infection however, only a small percentage of HIV-infected individuals (~2%) is able to mount this type of humoral response and the lymph node (LN)-specific parameters associated with such outcomes in the context of persistent viremia remain to be elucidated. To address this question, we performed a detailed analysis of the topology and immunophenotype of LN-resident CD4 T-cell and B-cell populations in viremic HIV+ volunteers with and without broadly neutralizing activity profiles.

**Methods:** LN cell suspensions and matched formalin-fixed, paraffin embedded (FFPE) tissue sections derived from chronically infected HIV+ individuals were analyzed using 30-colour multiparametric flow cytometry and quantitative multiplexed confocal imaging. Neutralization activity of matched serum samples was determined using a single-round infectivity assay. Breadth

of neutralization was defined by calculating the percent of HIV-1 Env-pseudoviruses that achieved an ID50 > 20

**Results:** The analysis of LN-architecture and germinal center (GC) topology revealed greater follicular GC disruption in HIV+ non-neutralizers compared to neutralizers as measured by total CD20hi/dim Ki67+ follicular area ( $p < 0.001$ ), light-zone (LZ)/dark zone (DZ) polarization and level of IgD+ involution. Neutralization activity was associated with an increased CD4+ T-cell memory (CD27 hi/lo CD45RO hi) frequency ( $p = 0.026$ ). Higher frequencies of activated (CD95+) ICOS+ and CD57+ expressing Tfh were also observed in neutralizers, consistent with potentially an increased capacity for optimal T-cell help. In addition, a lower frequency of unswitched CD27hi IgD+ memory B cells was found in neutralizers compared to non-neutralizers when B-cell populations were examined ( $p = 0.030$ ).

**Conclusion:** Neutralizing activity is associated with a greater degree of follicular GC preservation in the LN of chronically infected HIV individuals, higher levels of Tfh differentiation and lower frequencies of unswitched memory B cells. Thus, the implementation of strategies directed at preserving GC architecture during viremia may hold particular promise for the generation of broadly neutralizing antibodies in individuals affected by HIV.

## 274 TISSUE LANDSCAPE OF HIV ANTIBODY NEUTRALIZATION SUSCEPTIBILITY

Antoine Chailion<sup>1</sup>, Chuangqi Wang<sup>2</sup>, Timothy Schlub<sup>3</sup>, Wen-Han Yu<sup>4</sup>, Douglas A. Lauffenburger<sup>2</sup>, Davey M. Smith<sup>1</sup>, Boris Juegl<sup>2</sup>

<sup>1</sup>University of California San Diego, San Diego, CA, USA, <sup>2</sup>Massachusetts Institute of Technology, Cambridge, MA, USA, <sup>3</sup>The University of Sydney, Sydney, Australia,

<sup>4</sup>Bilkent University, Ankara, Turkey

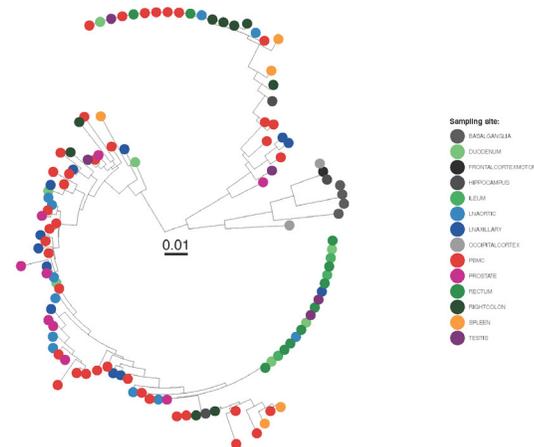
**Background:** HIV-1 genetic diversity and the presence of archived provirus that harbors escape mutations to antibodies are major obstacles for the clinical use of broadly neutralizing antibodies (bNAbs) to treat HIV-1 and for the use of bNAbs as interventions to clear reservoirs. This study aimed to characterize the viral reservoir to its susceptibility to antibody neutralization across peripheral blood mononuclear cells and deep tissues.

**Methods:** We analyzed near full length HIV env sequencing data generated from antemortem blood and postmortem tissues from participants in the Last Gift autopsy cohort using a Bayesian machine-learning model. The model uses HIV-1 envelope protein sequences and approximates glycan occupancy information as variables to quantitatively predict the half maximal inhibitory concentrations (IC<sub>50</sub>) of bNAbs. Using linear mixed effect models, this allowed us to map the landscape of neutralization resistance across each person's tissue reservoirs for 9 distinct bNAbs (targeting the CD4 binding site, V3-glycan, V2-apex and MPER) and grouped tissue sites (i.e. central nervous system [n=4 sites], genital tract [n=4], gut [n=8] and lymph nodes [n=9]) within and across participants.

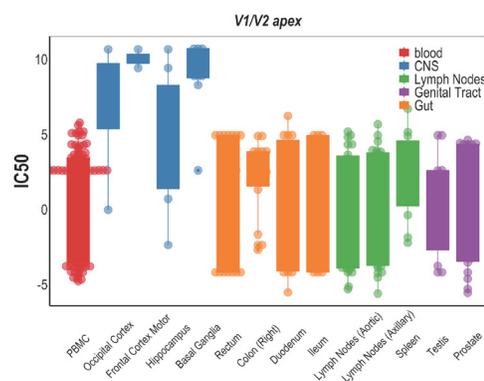
**Results:** We analyzed a total of 655 Env sequences (mean 109 [95%CI:72.7-145.6]/participant) across 32 distinct blood and tissue sites (mean 20 [95%CI:14.4-26.6] sequences/site) from 6 participants. We observed expected heterogeneity of predicted neutralization susceptibilities across participants but also across bNAb classes and tissues within participants. Neutralization susceptibilities were within the ranges that have been described for each tested bNAb, but for some antibodies, targeting the V2-apex or the V3-glycan, the predicted neutralization pattern differed between tissue compartments ( $p < 0.001$ ). In 5 participants that had remained suppressed on ART until their death, the breadth of neutralization susceptibilities in the PBMC reservoir did not differ from what was found in tissues. This observation was consistent across antibody target classes ( $P > 0.1$ ).

**Conclusion:** In persons with HIV (PWH) suppressed by ART, the landscape of predicted viral resistance to bNAb neutralization in the PBMC reservoir seems to match to what is observed in tissues. These data suggest that sampling the blood might be sufficiently representative of the diversity of the viral reservoir within an PWH to facilitate the selection of personalized bNAb combinations for therapeutic approaches.

Figure. Phylogeny of HIV-1 full length env variants (A) and bNAs susceptibility across compartments for V1/V2 apex (B) for one Last Gift participant. A.



B.



## 275 ANTIBODY PROFILING IDENTIFIES ANTIBODY TARGETS ASSOCIATED WITH NATURAL HIV CONTROL

Athena Chen<sup>1</sup>, Kai Kammers<sup>2</sup>, Daniel Monaco<sup>2</sup>, Sarah E. Hudelson<sup>2</sup>, Wendy Grant-McAuley<sup>1</sup>, Richard Moore<sup>2</sup>, Galit Alter<sup>3</sup>, Steven G. Deeks<sup>4</sup>, Charles Morrison<sup>5</sup>, Leigh A. Eller<sup>6</sup>, Joel Blankson<sup>2</sup>, Oliver Laeyendecker<sup>7</sup>, Ingo Ruczinski<sup>1</sup>, Harry B. Larman<sup>2</sup>, Susan Eshleman<sup>2</sup>

<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA, <sup>5</sup>FHI 360, Durham, NC, USA, <sup>6</sup>US Military HIV Research Program, Bethesda, MD, USA, <sup>7</sup>National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA

**Background:** HIV viral suppression is associated with delayed disease progression and reduced transmission. HIV controllers suppress HIV viral load to low levels without antiretroviral treatment (ART). We used a massively-multiplexed antibody profiling system (VirScan) to compare the antibody profiles in HIV controllers, viremic non-controllers, and non-controllers who were suppressed on ART. The VirScan assay provides quantitative information on antibody binding to >3,300 peptides spanning the HIV genome.

**Methods:** Antibody reactivity was assessed in 13 elite controllers, 27 viremic controllers, 21 non-controllers who were virally suppressed on ART, and 12 viremic non-controllers (Discovery Cohort). Antibody reactivity to selected peptides was quantified in a second cohort that included 29 elite controllers and 37 non-controllers who were virally suppressed on ART (Validation Cohort). Antibody reactivity was also assessed in 298 samples from 53 non-controllers who had viral load data from longitudinal visits that was used to determine viral load set point.

**Results:** In the Discovery Cohort, we identified 62 peptides that were preferentially targeted in HIV controllers compared to non-controllers. In the Validation Cohort, combined antibody reactivity to these peptides was also higher in elite controllers compared to non-controllers who were virally

suppressed on ART. The reactivity of antibodies to the 62 peptides was similar among HIV controllers who did or did not have the protective HLA-B\*57 allele. All but one of the 62 peptides were grouped into seven clusters of homologous peptides. The clusters were located in gp120 (two clusters), gp41, p17, p24, vpu, and integrase. Higher antibody reactivity to a subset of the peptides in the p17 cluster was significantly associated with lower viral load set points in the group of longitudinally-followed non-controllers.

**Conclusion:** A comprehensive, unbiased assessment of antibody reactivity to HIV peptides spanning the viral genome identified clusters of homologous peptides that were preferentially targeted in HIV controllers and non-controllers who had lower viral load set points. Further research is needed to characterize antibodies that target these peptides and evaluate T cell targeting of these epitopes. This research will provide new insights into natural control of HIV infection and may inform research on immune-based interventions for HIV prevention and treatment.

## 276 AUTOLOGOUS NEUTRALIZING ANTIBODIES INCREASE WITH EARLY ART AND SHAPE HIV REBOUND

**Elmira Esmaeilzadeh**<sup>1</sup>, Behzad Etemad<sup>1</sup>, Lavine L. Christy<sup>2</sup>, James Regan<sup>1</sup>, Colline Wong<sup>1</sup>, Abbas Mohammadi<sup>1</sup>, Elizabeth Connick<sup>3</sup>, Paul Volberding<sup>4</sup>, Michael Seaman<sup>2</sup>, Jonathan Li<sup>1</sup>

<sup>1</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>2</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA, <sup>3</sup>University of Arizona, Tucson, AZ, USA, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA

### Background:

Early initiation of antiretroviral therapy (ART) alters viral rebound kinetics after treatment interruption (TI) and may play a role in reducing the barrier to HIV remission. However, little is known about the underlying mechanisms and the selection of rebounding variants. Autologous neutralizing antibodies (aNAbs) represent a key adaptive immune response against a broad range of viruses and in this study, we evaluated whether aNAb responses could develop in the setting of early-ART initiation and investigated their role in shaping post-TI HIV rebound variants.

### Methods:

We performed single-genome amplification of HIV-1 env from pre-ART and post-TI plasma samples of 5 participants from the ACTG 371 study of early-treated individuals. aNAb activity was quantified using pseudoviruses from the most common plasma sequences and the serum dilution that inhibits 50% of viral infections (ID50) was determined.

### Results:

We tested the ability of pre-ART and post-TI plasma to neutralize env pseudoviruses derived by obtaining a median of 52 single-genome sequences from pre-ART and post-TI time points. Pre-ART, the median viral load was 33,1111 copies/ml and only weak aNAb activity was detected of pre-ART plasma against pre-ART virus. All participants were virologically suppressed (median 44 weeks) prior to TI. aNAb responses matured significantly while on suppressive ART as early post-TI plasma (median 8 weeks post-TI) demonstrated significantly improved neutralizing activity compared to pre-ART plasma (pre-ART vs early post-TI ID50 plasma neutralizing titers [1/x]: median 20 vs 432, P=0.007). Post-TI aNAb responses exerted selective pressure on the rebounding viruses as the HIV variants detected during TI were significantly more resistant to post-TI plasma neutralization compared to pre-ART virus (early post-TI plasma neutralization titers [1/x]: 432 vs 37, P=0.046). Compared to the pre-ART time point, viral diversity was also restricted during the TI (average pairwise distance of pre-ART vs post-TI plasma viruses: 0.09% vs 0.16%).

### Conclusion:

Early initiation of suppressive ART allows for the strengthening and maturation of the anti-HIV autologous neutralizing antibody response. Rebounding HIV variants are more resistant to contemporaneous neutralization, suggesting that viral variants contributing to viral rebound do not arise purely from a stochastic process, but are shaped by host immune pressures, including aNAb responses.

## 277 FORCED RESIDENCY OF T CELLS IN VIREMIC TISSUES DOES NOT INDUCE CONTROL OF SIV VIREMIA

**M. Betina Pampena**<sup>1</sup>, Leticia Kuri-Cervantes<sup>1</sup>, Sadia Samer<sup>2</sup>, Meagan Watkins<sup>3</sup>, Ronald S. Veazey<sup>3</sup>, Katharine J. Bar<sup>1</sup>, Brandon Keele<sup>4</sup>, Miles P. Davenport<sup>5</sup>, Mirko Paiardini<sup>6</sup>, Michael Betts<sup>1</sup>

<sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Northwestern University, Chicago, IL, USA, <sup>3</sup>Tulane National Primate Research Center, Covington, LA, USA, <sup>4</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA, <sup>5</sup>Kirby Institute, Sydney, Australia, <sup>6</sup>Yerkes National Primate Research Center, Atlanta, GA, USA

**Background:** HIV and SIV infected CD4+ T cells localize primarily to mucosal and lymphoid tissues (LT), which are also a major site for maintenance and subsequent recrudescence of the long-term HIV reservoir. Cytotoxic CD8+ T cells are critical for control of HIV and SIV viremia but the most potent peripheral blood cytotoxic CD8+ T cells are rarely found in LT, indicating that they seldom have the opportunity to interact with infected CD4+ T cells. Here, we assessed the impact of LT CD8+ T cells on SIV immunopathogenesis by inhibiting cell egress from LT in viremic rhesus macaques (RM) using the lymphocyte migration inhibitor FTY720. We hypothesized that the retention of recirculating CD8+ T cells in LT may enable local differentiation into cytotoxic effector cells with a subsequent impact on plasma viral load.

**Methods:** Four RM were infected intravenously with SIVmac239, and treated with FTY720 daily from day 7 or 28 until day 90 post-infection. Separately, fourteen acutely infected RM were treated with antiretrovirals (since day 14 post infection) for 6 months followed by treatment interruption while seven of them were receiving FTY720. Peripheral blood and lymph node (LN) samples were collected for flow cytometry analyses and viral load quantification.

**Results:** We observed near complete redistribution of circulating T cells into tissues within 28 days of FTY720 treatment (436±346 vs 75±62 CD8+ T cells/μl; and 610±462 vs 4±3 CD4+ T cells/μl). Despite the FTY720-induced retention of CD8+ T cells in LT, no beneficial effect was observed on peak viremia or set point during acute infection, nor time or degree of viral rebound after antiretroviral treatment interruption. FTY720-enforced tissue retention promoted an increase in the frequency of SIV-specific CD8+ T cells in LN of FTY720-treated RM after antiretroviral treatment interruption (p=0.035, vs control RM). However, the frequency of perforin+ granzyme B+ cells within LN SIV-specific CD8+ T cells remained low (1±1% vs 2±2%, pre vs post FTY720). Furthermore, FTY720 treatment did not increase the frequency of follicular homing CXCR5+ SIV-specific CD8 T cells.

**Conclusion:** These data indicate that simply increasing the number of CD8+ T cells in LT is insufficient to enable viral control in the SIV model. Moreover, enforced retention of CD8+ T cells in viremic tissues does not enable the acquisition of cytotoxic properties, suggesting that secondary signals not present in LT may be necessary to promote or maintain cytotoxic CD8+ T cell differentiation.

## 278 CD8+ RESIDENT MEMORY T CELLS CONTROL THE HIV RESERVOIR IN THE CERVICAL MUCOSA

**Nuria Massana**<sup>1</sup>, Jon Cantero-Pérez<sup>1</sup>, Marina Suppi<sup>1</sup>, Judith Grau-Expósito<sup>1</sup>, Josep Castellví<sup>2</sup>, Laura Mañalich-Barrachina<sup>3</sup>, Cristina Centeno-Mediavilla<sup>3</sup>, Vicenç Falcó<sup>1</sup>, Maria José Buzón<sup>1</sup>, Meritxell Genescà<sup>1</sup>

<sup>1</sup>Vall d'Hebron Research Institute, Barcelona, Spain, <sup>2</sup>Department of Pathology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain, <sup>3</sup>Department of Obstetrics and Gynecology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

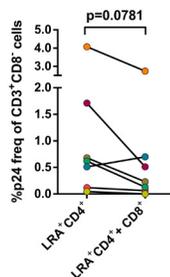
**Background:** The major hurdle to HIV-1 eradication is the establishment of viral reservoirs. CD8+TRM constitutively express cytotoxic molecules and their profile indicates that antiviral defense and target cell destruction represent key functions of these cells. Here we aimed to address the functional capacity of HIV-specific and non-specific CD8+TRM from the cervical mucosa in limiting HIV viral persistence.

**Methods:** CD8+TRM cells from cervical tissues were phenotyped by FACS (n=9). In ART-suppressed HIV+ women (n=8), we determined total vDNA in blood and cervix and its correlation with the frequency of cervical CD8+TRM, as well as Gag-specific CD8+TRM in cervical biopsies (n=7). 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 evaluate non-specific natural capacity of CD8+TRM in limiting the reactivated viral reservoir, an ex vivo latency model using IL-7 was established using

cervical explants from uninfected women. Natural cytotoxicity was measured by simultaneously determining p24 expression and cell-associated HIV-1 DNA in reactivated CD4+T cells in the presence or not of autologous CD8+TRM from uninfected tissue.

**Results:** Cervical CD69+CD8+T cell profile was compatible with >90% belonging to bona fide TRM. Further, CD8+TRM in cervical tissue represented >90% of CD69+CD8+T cells, and cervical samples from ART-suppressed patients had higher frequencies of CD8+TRM ( $p<0.05$ ) and non-TRM ( $p<0.01$ ). The frequency of cervical CD8+TRM cells correlated with proviral HIV-1 DNA in cervix ( $n=7$ ;  $p=0.03$ ) and blood ( $p=0.05$ ). 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. The latency model evidenced a natural capacity of CD8+TRM to reduce p24+ cells after reactivation ( $n=7$ ;  $p=0.08$ ; Figure), which, in cases of higher cell yield recovery, was associated with a decrease of the total reservoir size.

**Conclusion:** CD8+TRM in cervix are associated with less proviral HIV-1 DNA and may exert a greater control of the reservoir than effector circulating CD8+T cells. A cervical latency model could be crucial to study how HIV tissue reservoir could be eliminated not only by enhancing HIV-specific CD8+TRM but also by promoting their natural cytotoxicity.



## 279 EVALUATING VIRUS-SPECIFIC CD8 T CELLS FROM MULTIPLE ANATOMICAL SITES

**Jennifer Simpson**<sup>1</sup>, Carly E. Starke<sup>2</sup>, Carol Vinton<sup>1</sup>, Alexandra Ortiz<sup>1</sup>, Amy Ransier<sup>3</sup>, Daniel C. Douek<sup>3</sup>, Jonah Sacha<sup>2</sup>, David A. Price<sup>4</sup>, Jason Brenchley<sup>1</sup>  
<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>2</sup>Vaccine and Gene Therapy Institute, Beaverton, OR, USA, <sup>3</sup>Vaccine Research Center, National Institutes of Health, Bethesda, MD, USA, <sup>4</sup>Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, Wales, United Kingdom

**Background:** Virus-specific CD8 T cells are critical for control of SIV and HIV viral replication. SIV infection in Rhesus macaques (*Macaca mulatta*) induces SIV-specific CD8 T cells expansion in the blood and multiple tissues. To further evaluate the mechanisms underlying the induction and maintenance of SIV-specific CD8 T cells, we determined the kinetics of SIV-specific CD8 T cells across multiple anatomical sites during acute infection, chronic infection and treatment with anti-retrovirals. Furthermore, we utilized an SIV-gag DNA vaccine to assess the induction of SIV-specific cells upon acute antigen exposure. Finally, we utilized cytomegalovirus (CMV) infected animals to compare the tissue distribution of virus-specific CD8 T cells between two viruses that induce a chronic infection in the host.

**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 in the animal facility. SIV-specific CD8 T cells were enumerated and sorted by FACS from the PBMCs, bronchoalveolar lavage (BAL) lymph nodes (LN), liver, spleen, colon and jejunum using MHC1 Pentamers. Next generation sequencing of TCR beta genes was performed to determine the clonotypic structure of antigen-specific CD8 T cells across tissues.

**Results:** Acute SIV exposure induces virus-specific CD8 T cells in peripheral blood and lymph nodes, while chronic viremia seems to be required for expansion in other tissues. This expansion is maintained after administration of antiretroviral therapy, with a tissue resident phenotype most common across the gastrointestinal tract. Finally, natural CMV infection induced CMV specific CD8 T cells predominantly in the PBMCs compared with other anatomical sites.

**Conclusion:** SIV-specific CD8 T cells can inhabit multiple anatomical sites upon both acute and chronic antigen exposure, with a small fraction developing a

tissue-resident phenotype. In comparison, CMV infection induces CMV-specific CD8 T cells primarily in the blood, suggesting distinct tissue distribution between different viruses that induce chronic infection. Clonotypic analysis reveals potential mechanisms involved in development of tissue-specific immunological phenomena during viral infections.

## 280 COMBINATION OF IMMUNE CHECKPOINT BLOCKADE INCREASES IL-2 IN HIV-SPECIFIC T CELLS

**Chris Y. Chiu**<sup>1</sup>, Judy Chang<sup>1</sup>, Ashanti Dantanarayana<sup>1</sup>, Ajantha Rhodes<sup>1</sup>, Vanessa Evans<sup>1</sup>, Rachel Pascoe<sup>1</sup>, Celine Gubser<sup>1</sup>, Lydie Trautmann<sup>2</sup>, Rémi Fromentin<sup>3</sup>, Nicolas Chomont<sup>3</sup>, Paul U. Cameron<sup>1</sup>, James McMahon<sup>4</sup>, Thomas A. Rasmussen<sup>1</sup>, Sharon Lewin<sup>1</sup>

<sup>1</sup>University of Melbourne, Melbourne, Australia, <sup>2</sup>Oregon Health and Sciences University, Portland, OR, USA, <sup>3</sup>Centre Hospitalier de l'Université de Montreal, Montreal, Canada, <sup>4</sup>Monash University, Melbourne, Australia

**Background:** In people with HIV (PWH), elevated expression of immune checkpoints (IC) persists despite ART, leading to T-cell exhaustion. We aimed to determine if blocking single or multiple IC would enhance HIV-specific T cell function ex vivo.

**Methods:** Bulk PBMC obtained from 11 PWH on suppressive ART were stimulated with either gag, nef or Cytomegalovirus, Epstein-Barr Virus and Influenza (CEF) peptides in the presence of blocking antibodies to six IC molecules, including CTLA-4, PD-1, PD-L1, TIM-3, TIGIT and LAG-3 or relevant isotype controls. Antibodies were tested alone, in all dual combinations and using a cocktail of all six antibodies. Intracellular cytokine staining was used to determine production of CD107a, IFN $\gamma$ , TNF $\alpha$  and IL-2 in total and subsets of CD4+ and CD8+ T cells. Fold changes (FC) for IC antibodies compared to isotype controls were obtained. Bliss independence model was used to determine if the effect was synergistic.

**Results:** We detected a significant increase in the percentage of cells expressing IFN $\gamma$  and TNF $\alpha$  but not IL-2 or CD107a following stimulation with gag and nef peptides. The addition of single IC antibodies or all six together led to minimal change in cytokine production. In contrast, we observed a statistically significant increase in the percentage of gag-specific cells expressing CD107a in the presence of anti-LAG-3 combined with anti-TIGIT (median fold change, FC compared to isotype controls 1.75x) and anti-CTLA-4 (median FC 1.38x) in HIV-specific CD4+ T cells. We also observed increased frequency of cells expressing IL-2 (median FC 1.26 – 2.17x) with combinations of CTLA-4, TIGIT, TIM-3, PD-L1 and LAG-3, in both HIV-specific CD4+ and CD8+ T cells. The largest FC increase in IL-2 was observed when anti-CTLA-4 was combined with any other antibodies, except anti-PD1.

**Conclusion:** Multiples combinations of two IC antibodies (including LAG-3, CTLA-4 or TIGIT) can enhance the frequency of polyfunctional HIV-specific T cells ex vivo in samples obtained from PWH on suppressive ART. The increased production of IL-2 with dual IC blockage could have a significant functional effect on both proliferation and cytotoxicity. Given the better safety profile of anti-LAG-3 and anti-TIGIT, these novel antibodies should be further explored in strategies to control HIV in the absence of ART.

## 281 SELECTIVE DEPLETION OF TIGIT-EXPRESSING MEMORY HIV-SPECIFIC CD8+ T CELLS IN HIV-1 AND cART

**Oscar Blanch-Lombarte**<sup>1</sup>, Dan Ouchi<sup>1</sup>, Julieta Carabelli<sup>1</sup>, Miguel Marin<sup>1</sup>, Esther Jiménez-Moyano<sup>1</sup>, Ruth Peña<sup>1</sup>, Adam Pelletier<sup>2</sup>, Aarthi Talla<sup>2</sup>, Ashish A. Sharma<sup>2</sup>, Judith Dalmau<sup>1</sup>, José Ramón Santos<sup>3</sup>, Rafick-Pierre Sékaly<sup>4</sup>, Bonaventura Clotet<sup>1</sup>, Julia G. Prado<sup>1</sup>

<sup>1</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>2</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>3</sup>ABIVAX, Paris, France, <sup>4</sup>Emory University, Atlanta, GA, USA

**Background:** The expression of inhibitory Receptors (iRs) blocks CD8+ T-cell activity in HIV-1 infection. Consequently, the control of iRs is critical for recovering CD8+ T-cell function. However, the alteration of iR expression by HIV-1 infection is not fully understood and essential to identify future immunotherapeutic targets.

**Methods:** With this aim, we selected PBMCs from early (Ei, n=24) and chronically HIV-infected individuals (n=24) with follow-up in a median of 3 (S1) and 10 years (S2) on suppressive cART. For comparison, we selected healthy controls (HC, n=24). We performed cytofluorimetrics combining iRs (TIGIT, PD-1, LAG-3, TIM-3 and CD39), functional (CD107a, IFN $\gamma$  and IL-2) and lineage markers (CD3, CD4, CD8, CD45RA, CCR7 and CD27) in basal, SEB and HIV-1

conditions. Moreover, we analyzed multivariate datasets using Flowjo, SPICE and R packages and we compared classical and unsupervised net-SNE single-cell analysis. We also evaluated iR candidates by short-term antibody blockade in CD8+s.

**Results:** Our data revealed the expansion of TIGIT in CM and TM CD8+s during HIV-1 ( $p < 0.05$ ). We observed a negative correlation between CD4+ counts and TIGIT expression in CD8+s ( $p < 0.05$ ,  $r = -0.58$ ). Single-cell analyses further delineated the increase of three differential clusters of CD8+s ( $p < 0.05$ , HC vs HIV-1) sharing effector and memory-like features together with TIGIT and TIM-3 expression. Also, single-cell analysis identified six differential clusters in response to SEB and five in HIV-1. These clusters decreased in frequency in HIV-1 infection and cART sharing memory and effector-like features, TIGIT expression and functional heterogeneity. Complementary to this, we observed a decrease of HIV-specific TIGIT CM CD8+s producing CD107a (Ei vs S2,  $p < 0.05$ ) and a depletion in response to SEB of TIGIT+TIM-3 Effector CD8+s producing CD107a (HC vs S2,  $p < 0.05$ ). Besides, TIGIT CM CD8+s with production of IFN $\gamma$  expanded upon cART in SEB (HC vs S2,  $p < 0.05$ ). Short-term antibody blockade of TIGIT and TIGIT+TIM-3 favoured the recovery of CD107a degranulation in CD8+s.

**Conclusion:** Our data point towards irreversible alterations of TIGIT expression in CD8+s with HIV-1 infection despite cART. These alterations were driven by the depletion of specific cellular clusters of CM and Effector CD8+s associated with antigen specificity and a loss of degranulation potential. We propose the targeting of TIGIT to recover degranulation activity in CD8+s.

**282 SIGLEC-9 DEFINES AND RESTRAINS AN NK SUBPOPULATION HIGHLY CYTOTOXIC TO HIV+ CELLS**

**Opeyemi S. Adeniji<sup>1</sup>**, Leticia Kuri-Cervantes<sup>2</sup>, Michelle Ho<sup>1</sup>, Kar Muthumani<sup>1</sup>, Michael Betts<sup>2</sup>, Mohamed Abdel-Mohsen<sup>1</sup>

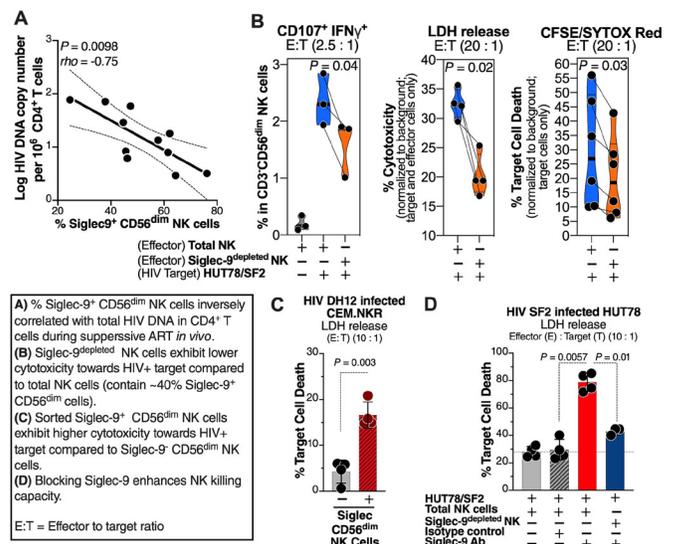
<sup>1</sup>Wistar Institute, Philadelphia, PA, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA

**Background:** Siglec-9 is an MHC-independent inhibitory receptor selectively expressed on a subset of the cytolytic CD56dim natural killer (NK) cells. Siglec-9 restrains NK cytotoxicity by binding to sialic acid glycans on the surface of target cells. Despite the importance of such Siglec-9 interactions in tumor immune evasion, their role during HIV infection has never been investigated.

**Methods:** We phenotypically characterized Siglec-9+ CD56dim NK cells from 45 donors: 10 HIV-negative controls; 11 HIV+ viremic; and 24 HIV+ on suppressive antiretroviral therapy (ART), using multiparametric cytofluorimetric analysis. We measured total HIV DNA in CD4+ T cells by qPCR. Next, we examined the functional ability of total, Siglec-9+, Siglec-9depleted, and Siglec-9- CD56dim NK cells (isolated from PBMCs of 3-6 healthy donors) to degranulate and kill cell lines (HUT78 and CEM.NKR) infected with HIV in the presence or absence of in-house Siglec-9 blocking antibody. Degranulation was measured as CD107a and IFN $\gamma$  co-expression on NK. Killing was evaluated by lactate dehydrogenase release and CFSE/SYTOX Red assays.

**Results:** Our phenotypic analysis showed that Siglec-9+ CD56dim NK frequency is 1) decreased during viremic HIV infection and remains decreased despite ART; and 2) inversely correlated with levels of CD4+ T cell-associated HIV DNA during ART ( $P < 0.01$ ). During viremic and ART-suppressed HIV infection, Siglec-9+ CD56dim NK cells exhibit an activated phenotype with higher frequencies of NK activating/cytotoxic receptors and markers (NKp30, CD38, CD16, DNAM-1, perforin) and lower expression of the inhibitory receptor NKG2A, compared to Siglec-9- CD56dim NK cells ( $P < 0.05$ ). Our functional analysis showed that total and Siglec-9+ NK cells produced more CD107a/IFN- $\gamma$  and exhibited higher cytotoxicity towards HIV+ cells, compared to Siglec-9depleted or Siglec-9- NK cells, respectively ( $P < 0.05$ ). Finally, blocking Siglec-9 enhanced NK cells' ability to degranulate and lyse HIV+ target cells ( $P < 0.01$ ). These effects were not observed using Siglec-9depleted NK cells.

**Conclusion:** Our data support a model in which Siglec-9+ CD56dim NK subpopulation, that has never been implicated during HIV infection, is highly cytotoxic against HIV+ cells but are being restrained by the inhibitory nature of the Siglec-9 molecule itself. Harnessing the cytotoxic capacity of Siglec-9+ CD56dim NK subpopulation, which is dampened by Siglec-9 expression, should be evaluated as a novel approach to control HIV infection during and/or post-ART.



**283 PROVIRAL BURDEN, GENETIC DIVERSITY, AND DYNAMICS DURING ART IN VIREMIC CONTROLLERS**

**Fredrick H. Omond<sup>1</sup>**, Hanwei Sudderuddin<sup>2</sup>, Aniqah Shahid<sup>1</sup>, Natalie N. Kinloch<sup>1</sup>, Bradley R. Jones<sup>2</sup>, Rachel L. Miller<sup>1</sup>, Olivia Tsai<sup>1</sup>, Daniel MacMillan<sup>2</sup>, Alicja P. Trocha<sup>4</sup>, Richard Liang<sup>2</sup>, Chanson Brumme<sup>2</sup>, Jeffrey B. Joy<sup>2</sup>, Bruce D. Walker<sup>4</sup>, Zabrina L. Brumme<sup>1</sup>

<sup>1</sup>Simon Fraser University, Burnaby, Canada, <sup>2</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, <sup>3</sup>University of British Columbia, Vancouver, Canada, <sup>4</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

**Background:** Viremic controllers can yield insights into HIV persistence, but they are underrepresented in reservoir dynamics studies. We combined single-genome sequencing (SGS), proviral quantification, phylogenetics and mathematical modeling to: i) reconstruct within-host pre-ART HIV evolutionary histories; ii) measure proviral burden, age and diversity on-ART and iii) estimate proviral half-lives in 4 viremic controllers.

**Methods:** Three participants broadly maintained pVL  $\sim 2000$ , while one eventually lost control, prior to initiating ART in chronic infection. We performed subgenomic HIV RNA SGS (nef) on a median of 12 longitudinal pre-ART plasma samples/participant. Two PBMC samples from a median of 1.1 and 1.9 years on ART were also analyzed: the first for reservoir quantification using the Intact Proviral DNA Assay (IPDA); and the second for proviral nef SGS. Proviral sequence ages were inferred using a phylogenetic approach that leverages within-host pre-ART HIV evolutionary rates; we then applied a published mathematical model of reservoir seeding and decay to infer host-specific proviral half-lives from these data.

**Results:** We collected 356 unique plasma HIV RNA sequences (range 52-173/participant) and 206 intact, non-hypermutated, unique proviral sequences (12-118/participant). All within-host phylogenies exhibited molecular clock signal pre-ART (range  $1.16 \times 10^{-5}$ – $5.35 \times 10^{-5}$  substitutions/base/day). Pre-ART pVL area under the curve correlated strongly with longitudinal pre-ART plasma HIV sequence diversity, total on-ART proviral burden and overall on-ART proviral diversity (all Spearman's  $\rho = 1$ ;  $p = 0.08$ ). Intact proviral %, quantified by IPDA, ranged from 10-94%, where the latter was observed in the individual who lost control prior to ART. For two participants, inferred proviral integration dates ranged from shortly following infection to cART initiation; for the other two, including the participant who lost control, proviruses largely dated well into chronic infection. For three of four participants, the best-fit proviral half-life estimates were  $< 1$  year, suggesting relatively rapid proviral turnover pre-ART; the fourth's proviral pool was consistent with negligible decay following deposition.

**Conclusion:** Despite their viremic control, significant within-host pre-ART HIV evolution nevertheless gave rise to diverse within-host proviral pools with varying intact genome burden. HIV eradication strategies must overcome within- and between-host diversity in proviral landscape.

## 284 HIV INTEGRATION INTO BACH2 AND STAT5B IS PREVALENT EARLY IN INFECTION

**Michael Dapp**<sup>1</sup>, Kristen Miller<sup>1</sup>, Marley Bishop<sup>1</sup>, Ann C. Duerr<sup>2</sup>, James I. Mullins<sup>1</sup>  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA

**Background:** Persistence of HIV despite ART remains a barrier to a cure. It is known that HIV proviruses are overrepresented in the BACH2 and STAT5B genes in persisting cells. Also, 9% and 31%, respectively, of individuals in chronic HIV infection have been reported to produce hybrid transcripts initiating in the HIV-LTR and spliced upstream of the gene start codon, thus subverting their regulation.

**Methods:** Single-copy sensitive nested PCR was used to identify hybrid transcripts in negatively selected CD4 cells from 44 individuals from the SABES/MERLIN primary infection cohort. This cohort enrolled uninfected MSM and transgender women in Lima, Peru between 2013 and 2015 and followed them for monthly HIV testing (Ab and RNA). Infected individuals started ART within 9 months of HIV acquisition. Hybrid transcripts were examined longitudinally for up to 4 years.

**Results:** A total of 179 samples with a median of  $1.6 \times 10^6$  CD4 cells (range  $3.3 \times 10^5 - 3.4 \times 10^6$ ) per sample were examined. 4,490 nested PCRs were performed, with the transcript structure of all 394 positive reactions confirmed by sequencing. In total, 19 of 44 individuals (43%) had detectable BACH2 hybrid transcripts and 30 of 44 (68%) had STAT5B hybrid transcripts, with 17 of 44 (39%) positive for both. In most cases, hybrid transcripts were detected at dilution endpoint (~4 copies per million CD4 cells). Given that each cell likely produces a large number of transcripts, the infected cell population with proviruses at STAT5B and BACH2 was likely much lower. Despite the strong stochastic component for positivity at such low levels, once hybrid transcripts were observed they were often found in later samplings (11/15 for BACH2 and 17/24 for STAT5B), indicating that proliferation maintained these cells in the ART-treated individuals. Finally, given the position and orientation requirements for hybrid transcripts detection and that all participants were treated early in infection, these data represent a significant underestimation of the fraction of HIV-infected individuals with HIV integrations in BACH2 and STAT5B.

**Conclusion:** HIV integration into BACH2 and STAT5B occurs in a large fraction of individuals early in infection. Cells producing hybrid transcripts are very likely to be maintained, albeit at low levels, by cell proliferation. Given that both genes are important regulators of T cell function, including T regulatory cell function, targeting these cells for elimination may be important for HIV cure strategies.

## 285 LONGITUDINAL ANALYSIS OF RESERVOIR DYNAMICS IN SIV-INFECTED MACAQUES ON LONG-TERM ART

**Emily J. Fray**<sup>1</sup>, Alexandra M. Bender<sup>1</sup>, John D. Ventura<sup>2</sup>, Po-Ting Liu<sup>2</sup>, Dan Barouch<sup>2</sup>, Janet Siliciano<sup>1</sup>, Robert Siliciano<sup>1</sup>

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA

**Background:** Rhesus macaques (RMs) infected with SIV are a critical model for HIV-1 infection of humans. Previous studies suggest the SIV latent reservoir stabilizes between 36–60 weeks on ART at a frequency of intact proviruses 1–2 logs higher than in people living with HIV-1 (PLWH). Similarly, full-genome sequencing indicates that APOBEC-mediated hypermutation is both more frequent and extensive and that intact proviruses represent a greater proportion of the reservoir. Longitudinal analysis of the frequency of intact and defective proviruses in PLWH has revealed differential decay kinetics of these 2 populations and points to potential mechanisms that contribute to reservoir persistence. However, analogous studies in SIV-infected macaques have been hampered by the short duration of ART and lack of methods to quantify defective genomes. It is therefore unclear how the size and composition of the SIV latent reservoir in RMs on long-term ART compares to the HIV-1 latent reservoir in humans.

**Methods:** Using the SIV intact proviral DNA assay and a novel assay to quantify hypermutated viral genomes we describe the first longitudinal analysis of the size and composition of the SIV latent reservoir in a cohort of 10 RMs on ART for >2 years. With this set of assays, we quantify the frequency of different types of viral DNA spanning 8 weeks to nearly 3 years on therapy and use this to determine the decay rate of each population.

**Results:** We found that the half-life of intact proviruses in SIV-infected RMs during the first 2 years on ART is approximately 12 months – much shorter than

the 44 months described for the HIV-1 latent reservoir. Hypermutated proviruses also decay but with a half-life of 29 months.

**Conclusion:** Our data shows that the SIV latent reservoir composition and size continue to change beyond the 1st year on ART – challenging previous assumptions that this pool stabilizes between 6 months and 1 year of therapy. The more rapid decay of intact relative to defective proviruses is consistent with observations in PLWH. Furthermore, the accelerated rate of decay for both types of proviruses relative to similar studies in PLWH suggests mechanisms underlying viral persistence may differ between SIV and HIV-1. These results provide essential benchmarks for researchers to evaluate the efficacy of interventions aimed at reducing the size of the latent reservoir in the SIV model and indicate that future studies must account for the decay that continues without interventions after the first year on ART.

## 286 DYNAMICS OF INTACT PROVIRAL SEQUENCES IN EARLY TREATED HIV-1 CLADE C–INFECTED INFANTS

**Catherine K. Koofhethile**<sup>1</sup>, Stefano Rinaldi<sup>2</sup>, Yelizaveta Rassadkina<sup>1</sup>, Vinh B. Dinh<sup>2</sup>, Ce Gao<sup>1</sup>, Suresh Pallikkuth<sup>2</sup>, Pilar Garcia-Broncano<sup>1</sup>, Lesley D. Armas<sup>2</sup>, Rajendra Pahwa<sup>2</sup>, Nicola Cotugno<sup>3</sup>, Maria Grazia Lain<sup>4</sup>, Paolo Palma<sup>3</sup>, Roger Shapiro<sup>5</sup>, Savita G. Pahwa<sup>2</sup>, Mathias Lichterfeld<sup>1</sup>

<sup>1</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>2</sup>University of Miami, Miami, FL, USA, <sup>3</sup>Bambino Gesù Children's Hospital, Rome, Italy, <sup>4</sup>Instituto Nacional de Saúde, Maputo, Mozambique, <sup>5</sup>Harvard TH Chan School of Public Health, Boston, MA, USA

**Background:** Understanding the mechanisms that allow HIV to persist long-term is important for advancing HIV cure research, specifically in infants who acquired HIV perinatally. We sought to evaluate longitudinally the genetic composition of the proviral reservoir in infants perinatally infected with HIV-1 Clade C.

**Methods:** We assessed the proviral reservoir in 6 infants from Mozambique who initiated ART within the first 2 months of life and were followed for a median of 23 (IQR 22–23.25) months. We used Full Length Individual Proviral Sequencing (FLIP-Seq) to evaluate the relative frequency and clonality of intact and defective proviruses over time.

**Results:** From the 6 infants, we obtained a cumulative total of 23 intact (11%) and 186 defective (89%) proviral sequences generated from a cumulative total of 51 million PBMCs over time. Four out of the 6 infants achieved virologic suppression (<200 HIV RNA copies/mL) following ART initiation and maintained viral suppression for the entire study period, while 2 of the infants experienced a transient loss of viral control at 8- and 11-months post ART initiation. We observed a gradual decline of total HIV copies during the observation period ranging from a median of 8.52 (IQR 4.39–36.56) HIV copies/10<sup>6</sup> PBMCs at the first sampling timepoint down to a median of 1.08 (IQR 0.28–3.12) HIV copies/10<sup>6</sup> PBMCs at the last sampling timepoint. Interestingly, this decline of HIV copies was more pronounced in intact proviruses which declined from a median of 0.72 (IQR 0–17.29) HIV copies/10<sup>6</sup> PBMCs at the first sampling timepoint to no detection at the last sampling timepoint. In one of the infants, we detected 4 clonal intact proviruses at 4 months post ART initiation and we also detected 4 members of the same clone 13 months later, indicating persistence of clonally expanded intact proviral sequences over a long period of time. In between these 2 time points, this infant displayed a short episode of rebound viremia of over 100,000 HIV RNA copies/mL. However, this rebound viremia did not affect the detectable composition of the intact proviral reservoir.

**Conclusion:** We observed a faster decline of intact proviruses in these infants, suggesting an increased vulnerability of intact proviral sequences to antiviral immune effects. Additionally, we observed clonal expansion of intact proviruses at early stages in pediatric HIV infection consistent with an important role of clonal proliferation of virally infected cells for virus reservoir homeostasis and maintenance.

## 287 CYTOKINE DYSREGULATION AND ANTIGEN RESPONSES DRIVE T-CELL EXPANSION IN HIV INFECTION

**Jack A. Collora**<sup>1</sup>, Siavash Pasalar<sup>2</sup>, Delia M. Pinto-Santini<sup>2</sup>, Neal Ravindra<sup>1</sup>, Javier R. Lama<sup>3</sup>, Carmela Ganoza<sup>4</sup>, Ricardo Alfaro<sup>3</sup>, Rachel Calvi<sup>1</sup>, Jennifer Chiarella<sup>1</sup>, Serena S. Spudich<sup>1</sup>, David Van Dijk<sup>1</sup>, Ann C. Duerr<sup>2</sup>, Ya-Chi Ho<sup>1</sup>  
<sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>Asociación Civil Impacta Salud y Educación, Lima, Peru, <sup>4</sup>Asociación Civil Impacta Salud y Educación, Lima, Peru

**Background:** Despite effective antiretroviral therapy (ART), HIV persists in CD4+ T cells which are maintained by clonal expansion. Even in virally suppressed individuals, HIV infection induces persistent immune dysfunction. Individuals receiving immediate ART have smaller size of HIV latent reservoir and lower levels of chronic immune activation. However, most individuals seek medical attention after 6 months of infection. We propose to identify drivers of T cell clonal expansion and immune dysfunction in HIV-infected individuals receiving delayed (versus immediate) ART as therapeutic targets.

**Methods:** From the SABES Study in which HIV infection was prospectively tested monthly, we obtained paired blood samples (during acute infection and after one year of suppressive ART) from 6 HIV-infected individuals (3 receiving immediate ART within 2 months of infection, 3 receiving delayed ART 6 months after diagnosis). Using single-cell ECCITEseq, we captured surface protein expression, transcriptome, HIV RNA, and T cell receptor sequences in the same single cells. We used machine learning algorithms to identify the impact of delayed ART on the gene expression profile of CD4+ T cells, determinants of T cell clone size, and markers differentiating clones containing HIV-RNA+ cells.

**Results:** We captured the single-cell multi-omics landscape of a total of 122,685 single cells (~8,179 cells per sample). Among them, we identified a total of 90 HIV-infected cells and 19 expanded CD4+ T cell clones harboring HIV-RNA+ cells. We found that interferon (IFN) responses are upregulated during viremia and returned to baseline after viral suppression, while T cell activation, immune exhaustion, and tumor necrosis factor (TNF) responses persisted despite one year of viral suppression in both immediate and delayed ART. Delayed ART upregulates cytokine regulation related genes such as ZFP36, DUSP2, and BHLHE40. While the major determinant of T cell clone size is antigen-response genes, the regulators of T cell clone size in delayed ART are immune exhaustion, IFN $\gamma$ , and TGF $\beta$  responses. Finally, HIV-RNA+ cells are enriched in proliferating Th1 effector cells.

**Conclusion:** We found that delayed ART induces persistent immune activation and dysregulated cytokine responses. HIV persists in Th1 effectors that proliferate secondary to persistent immune activation. Our study suggests that reducing chronic HIV antigen stimulation and cytokine dysregulation may potentially reduce the clonal expansion of HIV-infected cells.

## 288 IMPACT OF REPRODUCTIVE AGING ON HIV PERSISTENCE IN CISGENDER MEN AND WOMEN WITH HIV

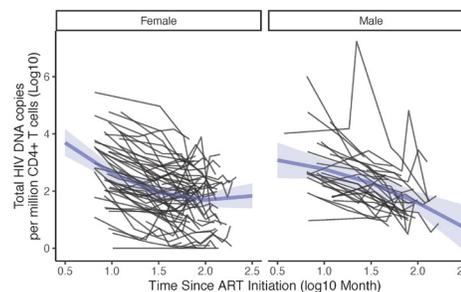
**Sara Gianella**<sup>1</sup>, Stephen A. Rawlings<sup>1</sup>, Masato Nakazawa<sup>1</sup>, Antoine Chaillon<sup>1</sup>, Matthew Strain<sup>1</sup>, Laura Layman<sup>1</sup>, Eileen P. Scully<sup>2</sup>, Brianna Scott<sup>1</sup>, Caitleen Pacis<sup>3</sup>, Kathleen Weber<sup>4</sup>, Alan Landay<sup>5</sup>, Christy Anderson<sup>1</sup>, Jonathan Karn<sup>6</sup>  
<sup>1</sup>University of California San Diego, San Diego, CA, USA, <sup>2</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>3</sup>University of California San Diego, La Jolla, CA, USA, <sup>4</sup>The Hektoen Institute, Chicago, USA, <sup>5</sup>Rush University, Chicago, IL, USA, <sup>6</sup>Case Western Reserve University, Cleveland, OH, USA

**Background:** Women represent the majority of HIV infections, yet sex differences in HIV reservoir dynamics during reproductive aging remain an under-explored area of research.

**Methods:** Longitudinal samples from virally suppressed cis-gender women (N=60, 285 samples) and men (N=31, 130 samples) were retrospectively identified from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) population. Participants were between the ages of 40-53 at the time of ART initiation and did not take hormonal therapy during analytic period. At each timepoint, levels of estradiol were measured by ELISA, cellular HIV DNA (total) and HIV RNA (unspliced and tatrev) were quantified by droplet digital PCR (ddPCR). Inducible HIV RNA was quantified on a subset of 132 samples from 11 participants by EDITS (measuring cell associated env mRNA after induction by TCR stimulation). We used mixed-effects model with a random participant intercept including normalized outcomes (total HIV DNA, HIV RNA and inducible HIV RNA) and sex, time since ART initiation, and the sex by time interaction as predictors.

**Results:** At baseline, median (IQR) CD4+ were 219 (82,324) cells/ul for women and 248 (120, 290) for men. Median age (IQR) was 45 (42,48) and 47 (43,51). Median follow up (IQR) was 93 (76,132) and 74 (52,93) months. As expected, levels of estradiol decreased among female participants (P<0.01). Overall, we observed a significant decline of total HIV DNA over time in both men and women (p<0.01). However, the rate of change significantly differed between sexes (p<0.01) with women having a significantly slower rate of decline as compared to men which becomes more pronounced with age (Figure 1). The levels of inducible HIV RNA increased over time in women but not in men during reproductive aging. We did not observe a difference in the dynamic of cell associated HIV RNA measures in the absence of ex vivo stimulation between sexes (p-values>0.17).

**Conclusion:** Previous work has demonstrated that the estrogen receptor is critical for the maintenance of HIV latency, but the intersection between aging and declining sex hormones is less clear. These studies demonstrate a sex specific HIV reservoir dynamic. While total HIV DNA (including intact and defective genomes) declines more slowly in women than in men, the inducible reservoir (enriched in replication competent virus) increases in women after menopause. The divergent behavior of the reservoirs in both sexes is an important parameter to be considered in cure trials.



**Figure Legend:** Longitudinal dynamic of total HIV DNA /  $10^6$  CD4+ T cells ( $\text{Log}_{10}$ ). Thin black lines represent individual participants. The thick blue lines and shaded regions indicate model-derived predicted values and their 95% confidence intervals.

## 289 SEX DIFFERENTIAL EXPRESSION OF IL-7 AND MARKERS OF HOMEOSTATIC PROLIFERATION

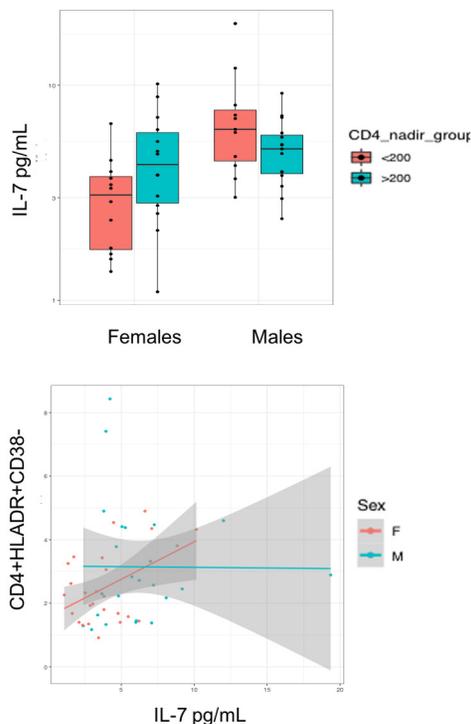
**Guido Massaccesi**<sup>1</sup>, Brittany White<sup>1</sup>, Monica Gandhi<sup>2</sup>, Rowena Johnston<sup>3</sup>, Jonathan Karn<sup>4</sup>, Nicolas Chomont<sup>5</sup>, Steven G. Deeks<sup>2</sup>, Eileen P. Scully<sup>1</sup>  
<sup>1</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA, <sup>3</sup>amfAR, New York, NY, USA, <sup>4</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>5</sup>University of Montreal, Montreal, Canada

**Background:** Reproductive age women have lower levels of residual virus activity with antiretroviral therapy, along with lower levels of T cell activation and PD-1 expression. The estrogen receptor is a regulator of latency reversal. T cell correlates of reservoir size and activity differ in men and women. We sought to assess the cytokine environment in matched men and women on suppressive ART to identify features of residual immune activation that may impact reservoir maintenance.

**Methods:** Plasma samples from a previously described matched cohort of males and females with HIV infection on suppressive ART (n=26F, 26M) were analyzed using the Human Cytokine-30Plex kit on the Mesoscale discovery multiplex platform. Analytes were assessed for relationship with reservoir size, activity, and T cell immune phenotype in men and women.

**Results:** Bivariate analysis identified 7 analytes with statistically significant sex-differential expression between males and females which included: IL-12, IL-17A, IL-6, IL-7, CCL17, LTalpha, and VEGF. Principle component analysis favored expression of IL-6 and IL-12 in females and the remainder in males. Of these analytes, IL-7 expression was also linked to history of AIDS as defined by CD4 nadir of <200. Plasma IL-7 levels were lower in women (p=0.004) and particularly among women with a CD4 nadir<200. IL-7 levels were positively correlated with CD4+HLADR+CD38- (Pearson's r=0.46, p=0.01) in females but not in males. CD8+HLADR+CD38- had a similar relationship that did not reach statistical significance (Pearson's r=0.35, p=0.080). There were no relationships between reservoir parameters (integrated and total HIV DNA, cell-associated HIV RNA, residual HIV viremia by single copy assay) and IL-7 in either sex.

**Conclusion:** Cytokine profile in ART-suppressed individuals identified lower expression of IL-7 among females, most pronounced when the CD4 nadir was <200. IL-7 expression was correlated with the CD4+HLADR-single-positive population associated with homeostatic proliferation in women, but not men. Declining estrogen levels post menopause have been linked to changes in IL-7 expression. These results suggest that homeostatic proliferation may have a differential contribution to reservoir maintenance in females and males. Further studies are needed to define whether these relationships changes with estrogen decline during reproductive aging.



## 290 TYPE I INTERFERON SIGNALING INDUCES HIV-1 LATENCY IN MACROPHAGES

Timothy Hanley<sup>1</sup>, Vicente Planelles<sup>1</sup>

<sup>1</sup>University of Utah, Salt Lake City, UT, USA

**Background:** The major obstacle to HIV cure is the existence of latent viral reservoirs – T cells and macrophages that harbor replication-competent, transcriptionally-silent proviruses. There remain crucial gaps in our understanding of the molecular mechanisms that lead to latent infection in macrophages. Prior studies from our laboratory have shown that interactions between macrophages and microbes that lead to type I interferon (IFN) production repress HIV-1 transcription, suggesting a central role for type I IFNs in establishing latent infection. We hypothesize that type I IFN signaling induces a state of transcriptional latency in HIV-1 infected macrophages by altering transcription factor recruitment to the viral promoter.

**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 that employs a reporter virus encoding nanoluciferase under the control of the 5' LTR. Transcription factor recruitment to the 5' LTR was evaluated using chromatin immunoprecipitation (ChIP). Single cell RNA sequencing (scRNA-Seq) was utilized to determine changes in gene expression in infected macrophages.

**Results:** We show that HIV-1 replication peaked early after infection in MDMs and steadily decreased over time. This decrease correlated with decreased transcription, suggesting that HIV-1 enters a latent state. This transition to latency was associated with decreased recruitment of NF- $\kappa$ B p65 and RNA polymerase II to the 5' LTR. Comparing productively-infected MDMs to latently-infected MDMs using scRNA-Seq revealed differential expression of a number of IFN-regulated genes (IRGs). Blocking type I IFN signaling partially reversed the decrease in HIV-1 expression, suggesting that type I IFNs produced by infected MDMs contribute to the repression of viral replication. Furthermore, treating

infected MDMs with type I IFNs led to a pronounced and sustained decrease in virus replication that simulated latency. Finally, blocking type I IFN signaling partially restored the interaction between NF- $\kappa$ B p65 and RNA polymerase II with the 5' LTR.

**Conclusion:** Our data suggest that type I IFN signaling, directly or indirectly, alters transcription factor recruitment to the HIV-1 promoter to induce a state reminiscent of 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.

## 291 MODULATION OF HIV TRANSCRIPTION USING AN IN VITRO MACROPHAGE HIV-1 LATENCY MODEL

Michelle E. Wong<sup>1</sup>, Chad J. Johnson<sup>2</sup>, Anna C. Hearn<sup>3</sup>, Anthony Jaworowski<sup>3</sup>

<sup>1</sup>Burnet Institute, Melbourne, Australia, <sup>2</sup>Monash University, Melbourne, Australia,

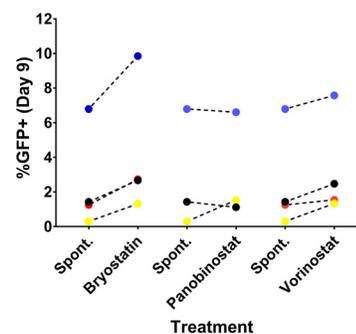
<sup>3</sup>RMIT University, Melbourne, Australia

**Background:** HIV-infected macrophages persist despite viral suppression and can contribute to viral rebound upon treatment interruption, yet little is known regarding the establishment and control of latency in this important HIV reservoir. Physiologically-relevant in vitro systems that provide a robust, quantitative model of latent infection and reactivation are required to investigate factors that govern latency in macrophages.

**Methods:** Primary human monocyte-derived macrophages (MDM) were infected in vitro with a GFP-HIV reporter virus and FACS sorted 7-days post-infection, to purify GFP- populations consisting of uninfected bystander and non-productively infected MDM. GFP- MDM were cultured for a further 9 days in media containing entry inhibitor enfuvirtide (T20), to prevent de novo infection, and potential latency modulating agents. Reactivation of HIV transcription was quantified by live cell fluorescent microscopy via expression of GFP in reactivated cells.

**Results:** Spontaneous reactivation of HIV transcription within MDM was observed in all donors with a linear rate of  $0.22\% \pm 0.04\%$  (mean  $\pm$  SEM, n=10) GFP+ cells per day, slower than rates of HIV transcription following initial infection ( $0.91\% \pm 0.12\%$  GFP+ cells per day), indicating the presence of a population of potentially latently infected macrophages. Reactivated MDM produced replication competent virus, demonstrated by infection of heterologous PBMC in co-culture and in a cell-free infection system. Polarization of MDM to either M1 or M2 significantly inhibited ( $p=0.03$ ) or enhanced ( $p=0.02$ ) HIV reactivation, respectively. HIV reactivation was increased in unpolished MDM by latency reversing agents (LRAs) including PKC agonist, bryostatin-1, and HDAC inhibitor vorinostat; however, the LRA panobinostat did not elicit reactivation in this model.

**Conclusion:** We have developed a robust and quantitative model of latently infected primary MDM, which can be used to advance cure strategies targeting the latent HIV reservoir. Our data suggest the potential of MDM to harbour latent HIV infection and contribute to viral rebound. The modulation of reactivation rates by polarization and latency reversing agents suggests latent macrophage reservoirs are sensitive to local environments in vivo, and may be therapeutically modulated. Moreover, the mechanisms governing latency in macrophages may differ to those in CD4+ T cells, potentially requiring macrophage-specific strategies to target HIV in these cells.



## 292 NOVEL CRISPR SCREENS IDENTIFY A ROLE FOR CUL3 IN HIV-1 LATENCY MAINTENANCE

Emily Hsieh<sup>1</sup>, Molly OhAinle<sup>2</sup>, Michael Emerman<sup>2</sup>

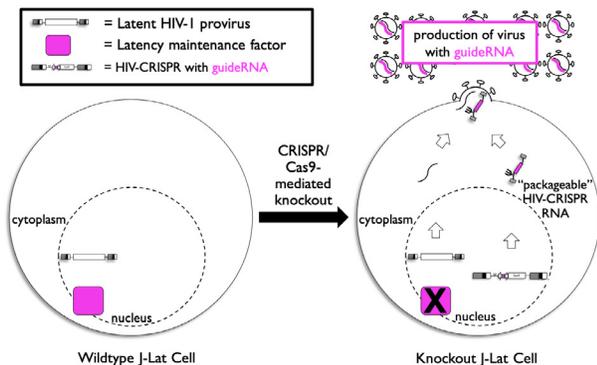
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA

**Background:** HIV-1 establishes long-lived latent reservoirs that present a barrier for virus eradication. One approach to reduce the latent reservoir is the use of latency reversal agents followed by the killing of virus-producing cells. However, this approach is limited by the inability to reactivate the majority of latent proviruses, highlighting the need for a greater understanding of the interplay of mechanisms involved in the maintenance of HIV-1 latency.

**Methods:** We initiated a multi-arm CRISPR screening approach in the J-Lat model of latent infection to gain a comprehensive representation of the pathways involved in HIV-1 latency. Upon CRISPR/Cas9-mediated knockout of a latency maintenance gene, the provirus of the J-Lat cell line is reactivated. The screen also adapts a functional CRISPR screening methodology developed in the Emerman lab called HIV-CRISPR. The HIV-CRISPR vector is a lentiviral vector that encodes Cas9, a library of single guide RNAs (sgRNA), and two intact LTRs that can be mobilized to produce an HIV-CRISPR RNA containing the sgRNA of interest in the presence of the reactivated HIV-1 provirus. The HIV-CRISPR RNA is packaged in trans into the reactivated virion and released into the supernatant. Sequencing is then used to quantify the enriched sgRNAs in the released viruses serving as a direct readout to identify genes controlling HIV-1 latency maintenance. We investigated the mechanisms controlling the chromatin state of latent HIV-1 by developing a custom sgRNA library specifically targeting ~800 human genes involved in some aspect of epigenetic control of gene regulation or DNA modification.

**Results:** The screen involving knockout of the epigenetics genes identified known HIV-1 latency maintenance factors including BRD4 and KAT5. Our top gene hit in the screen was Cullin 3 (CUL3), which is involved in ubiquitination of target proteins, and novel to HIV-1 latency. Knockout of CUL3 in two different J-Lat clones leads to the release of HIV-1 from latency. Similar experiments in primary CD4+ T-cell models of HIV-1 latency are ongoing.

**Conclusion:** We developed a new high-throughput, combination latency HIV-CRISPR screen that is able to identify novel and known HIV-1 latency maintenance genes. Initial validation of the screen demonstrates that protein ubiquitination through the CUL3 pathway is important for HIV-1 latency maintenance. Further analysis and combining the results from additional screens will provide a more comprehensive view of HIV-1 latency.



## 293 SYNERGISTIC COMBINATIONS OF LATENCY-REVERSING AGENTS IDENTIFIED USING CRISPR SCREENS

Weiwei Dai<sup>1</sup>, Fengting Wu<sup>1</sup>, Joseph Varriale<sup>1</sup>, Hao Zhang<sup>2</sup>, Janet Siliciano<sup>1</sup>, Wei Li<sup>3</sup>, Robert Siliciano<sup>1</sup>

<sup>1</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>3</sup>Children's Research Institute, Children's National Health System, Washington, DC, USA

**Background:** HIV-1 persisting in a latent form in resting CD4+ T cells despite effective antiretroviral therapy is the major barrier to cure. A promising therapeutic approach known as "shock and kill" seeks to achieve cure by sequentially reversing latency in infected cells and then promoting the killing of productively infected cells. To date, however, no single LRA has been shown to reduce latent reservoir size in infected individuals. Functional genetic screening, especially CRISPR/Cas9-based screening, provides a global unbiased approach

to understand the molecular aspects of HIV-1 infection. However, few studies focused on systematically identifying LRA combinations that overcome the limitations of individual LRAs.

**Methods:** We established a polyclonal in vitro model for HIV-1 latency. HIV-1 gene expression can be re-induced in >90% of this population by TNF- $\alpha$  treatment as evidenced by GFP expression. To identify candidate drug targets that potentially synergize with existing LRAs, we performed genome-wide CRISPR screening followed by induction of HIV-1 gene expression in latently infected cells using a suboptimal dose of a selected LRA, and then sorted for GFP+ cells directly. A gene whose knockout leads to enhanced GFP expression may emerge as the candidate drug target for synergy with the stimulating LRA if inhibitors of its function exist.

**Results:** We tested this approach using the SMAC mimetic AZD5582, an inhibitor of the non-canonical NF-kappa b (nNF- $\kappa$ B) pathway, as an LRA and identified HDAC2, a histone deacetylation complex blocked by some HDAC inhibitors and BRD2, part of the Bromodomain and Extra-Terminal motif (BET) protein family that are targeted by BET inhibitors. Using CD4+ T cells from individuals on antiretroviral therapy, we confirmed synergy between AZD5582 and several HDAC inhibitors and between AZD5582 and the BET inhibitor JQ1. Remarkably, a reciprocal screen using an HDAC inhibitor as an LRA identified nNF- $\kappa$ B regulators, especially BIRC2, as a druggable synergistic candidate for use in combination with HDAC inhibition, confirming the validity of this approach.

**Conclusion:** Our studies provide novel insights into the roles of host factors in HIV-1 reactivation and validate a system for finding drug combinations for HIV-1 latency reversal.

## 294 ACTIVATING PKC- $\epsilon$ INDUCES HIV EXPRESSION WITH IMPROVED TOLERABILITY

Alivelu M. Irrinki<sup>1</sup>, Jasmine Kaur<sup>1</sup>, Bally Randhawa<sup>1</sup>, Hongxia Li<sup>1</sup>, Ryan McFadden<sup>1</sup>, Chelsea Snyder<sup>1</sup>, Hoa Truong<sup>1</sup>, Daniel Soohoo<sup>1</sup>, Chad Greco<sup>1</sup>, Eric Hu<sup>1</sup>, Helen Yu<sup>1</sup>, Bernard Murray<sup>1</sup>, Wade Blair<sup>1</sup>, Tomas Cihlar<sup>1</sup>, Jeffrey Murry<sup>1</sup>

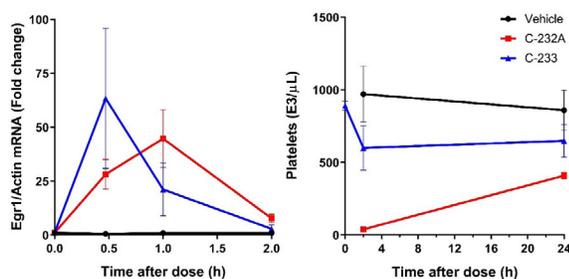
<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Activation of latent HIV could increase elimination of infected cells by therapeutics that directly target infected cells or stimulate antiviral immunity, potentially leading to long-term remission or cure. Protein kinase C (PKC) agonists are highly effective at activating latent HIV in vitro. We previously found that platelet activation is associated with toxicity of novel PKC agonist C-232A and that this critical safety liability is broadly associated with known classes of PKC agonists. We hypothesized that specific targeting of PKC isoforms abundant in T cells but not in platelets could improve tolerability of PKC agonists that activate HIV.

**Methods:** PKC isoform expression in T cells and platelets was measured by western blot to identify differentially expressed isoforms. Isoform-selective agonists were identified by testing compounds for individual PKC isoform translocation. HIV RNA was assessed after treatment in cells isolated from ART-suppressed people living with HIV. In latently infected Jurkat cells, HIV induction was assessed by flow cytometry after expression of constitutively active PKC isoforms. In vivo platelet activation was assessed by hematology counts and T cell activation by EGR1 and CD69 mRNA quantification from whole blood in rats.

**Results:** Prostratin induction of HIV was unaffected by Gö6976, an inhibitor of classical PKC isoforms (PKC- $\alpha/\beta/\gamma$ ), indicating that novel PKC isoforms (PKC- $\delta/\epsilon/\eta/\theta$ ) are sufficient for HIV activation. Expression analysis revealed high levels of PKC- $\theta$  and  $\delta$  in platelets and T cells while PKC- $\eta$  and  $\epsilon$  were only abundant in T cells. In Jurkat cells, PKC- $\epsilon$  was sufficient for HIV activation, supporting selective targeting of PKC- $\epsilon$  to reduce toxicity. Systematic modification of C-232A led to the identification of C-233, a novel PKC agonist 2-fold and 10-fold more selective for PKC- $\epsilon$  over PKC- $\theta$  and PKC- $\delta$ , respectively. In rats, C-233 and C-232A increased Egr1 mRNA associated with T cell activation to similar levels, but C-232A affected platelet levels more severely than C-233. One of 6 animals treated with C-232A was euthanized, but no deaths occurred with C-233.

**Conclusion:** Platelet activation is a critical safety liability associated with non-selective PKC agonists and should be carefully monitored in preclinical and clinical studies. These results indicate that specifically activating PKC- $\epsilon$  might improve safety in vivo and support continuing structure-based design of selective novel PKC agonists for safe activation of HIV reservoirs.



## 295 VENETOCLAX SIGNIFICANTLY REDUCES HIV VIRAL LOAD IN VIVO AND IN VITRO

Aswath Padmanabhan Chandrasekar<sup>1</sup>, Nathan W. Cummins<sup>1</sup>, Sekar Natesampillai<sup>1</sup>, Anisha Misra<sup>1</sup>, Alecia Alto<sup>1</sup>, Andrew D. Badley<sup>1</sup>

<sup>1</sup>Mayo Clinic, Rochester, MN, USA

**Background:** The BCL-2 pro-survival protein has been implicated in HIV persistence, and we have previously demonstrated that the clinically used BCL-2 inhibitor Venetoclax augments HIV induced killing of the reactivating cell, in vitro. It is unknown whether Venetoclax impacts HIV dynamics in vivo. We hypothesized that Venetoclax would reduce HIV replication in a murine model of HIV, and increase clearance of HIV infected cells by cytotoxic T Cells.

**Methods:** Primary CD4 T-Cells isolated from HIV infected, ART suppressed, donors were infected in vitro with HIV IIIB, subsequently treated with the BCL2-specific inhibitor Venetoclax, and co-cultured with HIV Pepmix expanded, CD8 T Cells, in the presence of ART. The CD8-negative target cells were analyzed by flow cytometry to measure cell death by Live/Dead staining and intracellular p24 expression. Supernatant p24 was measured by ELISA to estimate viral production. Using NOD/Shi-scid/IL-2Rnull immunodeficient (NCG) mice, humanized using CD34+ cells isolated from human cord blood, we treated HIV infected CD34+ cell humanized mice with or without Venetoclax and assessed viral dynamics in the absence of ART, measured by HIV RNA PCR.

**Results:** Treatment of acutely HIV-infected CD4 T-Cells with the BCL-2 inhibitor Venetoclax significantly increased susceptibility to Cytotoxic T lymphocyte killing at E:T ratios of 1:2 and 1:5 ( $p < 0.05$ ), accompanied by significant reductions in levels of supernatant p24 ( $p < 0.05$ ). Within our in-vivo mouse model, BCL-2 inhibition resulted in significant, log fold decreases in HIV RNA with Venetoclax ( $p = 0.002$ ), accompanied by significant decreases in CD4 cells ( $p < 0.0001$ ) compared to control.

**Conclusion:** Taken together, these findings suggest that Venetoclax augments host immune function against HIV, in the setting of active HIV infection, both in an in-vitro and in-vivo setting. These findings represent a significant step forward in our understanding of the clinical applicability and feasibility of BCL-2 inhibition for HIV therapy.

## 296 AUTOLOGOUS VIRUS-NEUTRALIZING ANTIBODIES DELAY VIRUS REBOUND IN INFANT SHIV MODEL

Stella J. Berendam<sup>1</sup>, Emilie A. Uffmann<sup>1</sup>, Tiffany M. Styles<sup>2</sup>, Veronica Obregon-Perko<sup>3</sup>, Amit Kumar<sup>1</sup>, Katharine J. Bar<sup>4</sup>, George Shaw<sup>4</sup>, Guido Silvestri<sup>2</sup>, Rama R. Amara<sup>2</sup>, Ann Chahroudi<sup>3</sup>, Sallie R. Permar<sup>1</sup>, Genevieve Fouda<sup>1</sup>

<sup>1</sup>Duke Human Vaccine Institute, Durham, NC, USA, <sup>2</sup>Yerkes National Primate Research Center, Atlanta, GA, USA, <sup>3</sup>Emory University, Atlanta, GA, USA, <sup>4</sup>University of Pennsylvania, Philadelphia, PA, USA

**Background:** Early ART improves disease outcomes in infected children but does not eliminate latent HIV reservoirs. Studies in a small subset of perinatally infected children who developed HIV-specific antibody responses and remained virus free when ART was interrupted, suggested that autologous antibody responses maybe important for sustained viral control and lack of virus rebound. However, kinetics of HIV-specific antibody responses and their impact on virus rebound in the setting of postnatal HIV transmission is unclear. We used an established infant rhesus macaque (RM) SHIV infection model with delayed ART to define the kinetics, specificity, breadth, and antiviral functions of HIV-specific antibodies in the setting of postnatal HIV infection.

**Methods:** 10 infant RMs were orally challenged with SHIV.C.CH505 375H dCT and daily triple ART initiated at 8wpi. ART was interrupted after 52 weeks and virus rebound was monitored by viral RNA detection in infant plasma. Antibody development was assessed by binding to the autologous virus CH505 TF gp120 and MN gp41. HIV epitope and clade specificities were assessed

using a multiplex luminex assay (BAMA). Plasma antibody neutralizing and non-neutralizing functions were evaluated at time points pre-ART, during ART, and ATI.

**Results:** HIV envelope (Env) gp120- and gp41-specific antibodies were first detected at 4wpi and decline after ART initiation (8wpi). Yet, the antibody levels remained detectable throughout ART. Plasma Env-specific antibodies predominantly targeted the V3-loop, C5 region, and showed broad reactivity against heterologous HIV Envs. Plasma antibody at pre-ART, during ART, and post-ATI mediated robust ADCP activity against CH505 TF-gp120-coated beads but limited ADCC activity against SHIV-infected cells at similar time points. 5 of 10 infants developed autologous virus neutralization while on ART. Upon ATI, virus rebound was observed in all infants (range, 7-35 days) except 1 infant that developed highest level of autologous plasma neutralization. Pseudoviruses generated using rebound Envs were resistant to autologous plasma neutralization. Computational machine learning analyses identified autologous neutralization as strongest predictor of delayed virus rebound.

**Conclusion:** Development of autologous virus neutralizing antibody may delay time to virus rebound. This study underscores the importance to explore augmentation of autologous virus neutralization as a potential strategy to afford viral remission or cure in pediatric HIV.

## 297 VIRUS REMISSION WITH AN OPTIMIZED EARLY ART REGIMEN IN MACAQUES

Michele B. Daly<sup>1</sup>, Mara Sterling<sup>1</sup>, Kenji Nishiura<sup>1</sup>, Angela Holder<sup>1</sup>, Chuong Dinh<sup>1</sup>, Alison Swaims Kohlmeier<sup>1</sup>, Sunita Sharma<sup>1</sup>, Jillian Condrey<sup>1</sup>, Rex A. Howard<sup>1</sup>, Patrick Mills<sup>1</sup>, James Mitchell<sup>1</sup>, Veele Van Eygen<sup>2</sup>, William R. Spreen<sup>3</sup>, Walid Heneine<sup>1</sup>, Gerardo Garcia-Lerma<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>Janssen, Beerse, Belgium, <sup>3</sup>ViiV Healthcare, Research Triangle Park, NC, USA

**Background:** Early initiation of antiretroviral therapy (ART) does not cure HIV in humans or SIV in macaques due to rapid viral reservoir establishment. Here, we investigated in macaques if a novel ART regimen, designed to have robust penetration in virus reservoir sites, can result in virus remission after treatment cessation.

**Methods:** The ART regimen included daily tenofovir alafenamide (TAF; 1.5 mg/kg), and emtricitabine (FTC; 20 mg/kg), and monthly rilpivirine long-acting (RPV LA; 200 mg/kg), and cabotegravir long-acting (CAB LA; 50 mg/kg) for 6 months followed by 6 months of CAB LA/RPV LA maintenance therapy. TAF was selected to enhance tenofovir-diphosphate (TFV-DP) levels in lymphoid tissues (LT). CAB LA and RPV both distribute in the central nervous system. TAF/FTC were given at human-equivalent doses and administered orally to mimic drug biodistribution in humans. CAB LA/RPV LA were given intramuscularly at doses that maintain human therapeutic drug levels. Macaques were infected intrarectally with RT-SHIV and initiated treatment at day 5-6 post infection (n=4) or were untreated (n=2). SHIV RNA in plasma was monitored by RT-PCR (LOQ=12.5 copies/ml) during 1 year of ART and a 20-month period of no treatment which included in vivo CD8+ cell depletion with monoclonal antibody MT807R1 at month 16. Drug concentrations were measured by HPLC-MS/MS.

**Results:** Peak viremia in treated animals was 3.4 [range=2.7-4.3] log<sub>10</sub> RNA copies/ml compared to 6.8-7.0 in untreated controls. Treated macaques achieved viral suppression 14-22 days after treatment initiation and remained aviremic during 1 year of ART and the 20-month follow-up period. Median plasma CAB levels during treatment were 2.11 ug/ml and became undetectable 3 months after the last dose. RPV testing is ongoing. Median concentrations of TFV-DP in PBMCs, LT, and RT were 1427 and 367 fmol/10<sup>6</sup> cells, and 14.6 fmol/mg of tissue, respectively. Median FTC-TP levels were 498 and 260 fmol/10<sup>6</sup> cells in PBMCs and LT, respectively, and were undetectable in RT. Treatment with MT807R1 effectively depleted >99.9% of CD8+ T cells in blood. Plasma SHIV RNA remained undetectable during and 4 months after CD8 depletion.

**Conclusion:** We identified in macaques a suppressive ART regimen that results in virus remission following early treatment. The lack of viral rebound 20 months after treatment cessation and CD8 depletion is encouraging and highlights the need to further define the effect of optimized early ART regimens on virus remission.

**298 EFFECT OF RECOMBINANT GROWTH HORMONE ON HIV RESERVOIRS: A PILOT STUDY (CTN 298)**

Isabelle Turcotte<sup>1</sup>, Amélie Pagliuzza<sup>2</sup>, Stéphane Isnard<sup>3</sup>, Cezar Iovi<sup>3</sup>, Rémi Fromentin<sup>2</sup>, Steven G. Deeks<sup>4</sup>, Mary Mahony<sup>5</sup>, Brooke Hayward<sup>5</sup>, Maryellen Craig<sup>5</sup>, Jean-Pierre Routy<sup>3</sup>, Nicolas Chomont<sup>1</sup>

<sup>1</sup>Université de Montréal, Montreal, Canada, <sup>2</sup>Centre de Recherche du CHUM, Montreal, Canada, <sup>3</sup>McGill University Health Centre, Montreal, Canada, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA, <sup>5</sup>EMD Serono, Rockland, MD, USA

**Background:** Administration of recombinant human growth hormone (rhGH) in ART-treated individuals has been shown to increase thymic output and CD4+ T cell counts. We hypothesized that the production of naïve T cells induced by rhGH may lead to the clearance of infected memory CD4+ T cells by repopulating the CD4+ T cell niche.

**Methods:** Twelve HIV-1-infected adults (<40 years of age) on stable ART were enrolled in an open-label single-arm study of rhGH therapy. rhGH was administered by subcutaneous injection on an outpatient basis for a total of 48 weeks (3 mg/day for 24 weeks, followed by 1.5 mg/day for 24 weeks). PBMCs were collected at baseline and every 12 weeks. In isolated CD4+ T cells, we measured thymic output [T Cell Receptor Excision Circles (TRECs) quantification by qPCR], as well as the size of the HIV reservoir by HIV DNA qPCR, tat/rev limiting dilution assay (TILDA) and a modified quantitative viral outgrowth assay (mQVOA).

**Results:** Most of the participants were male (10 males, 2 females), with a median age of 34 years and a median duration of ART of 3.7 years. No serious adverse events were reported. However, nine participants discontinued rhGH therapy before 48 weeks, most commonly due to musculoskeletal pain (n=6), which resolved after drug discontinuation. To assess the effects of rhGH, we compared baseline values to measures performed at the last visit on active drug and at which PBMCs were available (n=10, mean duration of rhGH therapy = 25 weeks). As expected, the frequency of TRECs in CD4+ T cells slightly increased (1.5 mean fold change; p=0.01), reflecting an increase in thymic output. However, absolute CD4 T cell counts remained unchanged. Administration of rhGH led to a modest but significant reduction in the frequency of CD4+ T cells harboring total HIV DNA (0.8 mean fold change; p=0.01). The frequency of CD4+ T cells with the ability to produce Tat/Rev transcripts upon stimulation remained stable. There was a trend for a decrease in the frequency of CD4+ T cells harboring replication competent HIV (mean fold reduction of 0.41 infectious units per million cells, p=0.08).

**Conclusion:** In this pilot study, administration of rhGH to individuals on ART led to a modest but statistically significant reduction in HIV reservoir markers despite early rhGH discontinuation in most participants. Reservoir reduction approaches based on a "fill to replace" strategy warrant further investigation.

**299 EFFECTS OF PD-1 BLOCKADE ON HIV RESERVOIRS IN BLOOD DURING ART**

Liliana Pérez<sup>1</sup>, Lauren B. Reoma<sup>2</sup>, Sean Patro<sup>3</sup>, Max Lee<sup>1</sup>, Prakriti Mudvari<sup>1</sup>, Bryan R. Smith<sup>2</sup>, Amanda Wiebold<sup>2</sup>, Jong Shin<sup>2</sup>, Ulisses Santamaria<sup>2</sup>, Tae-Wook Chun<sup>1</sup>, Susan Moir<sup>1</sup>, Mary F. Kearney<sup>3</sup>, Avindra Nath<sup>2</sup>, Eli A. Boritz<sup>1</sup>

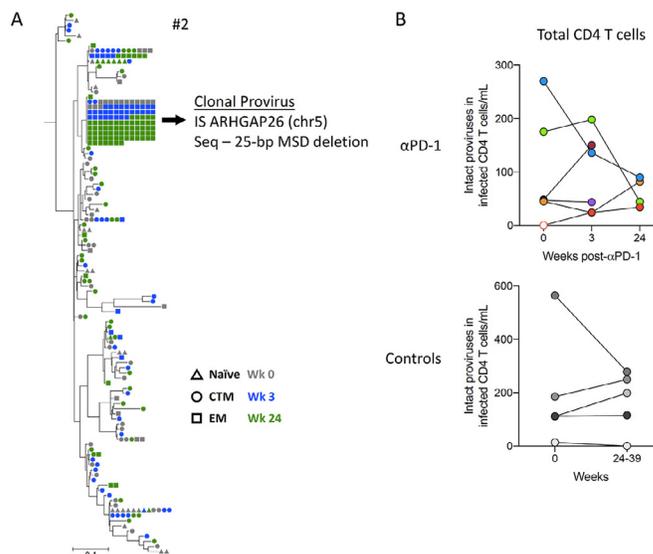
<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>2</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, <sup>3</sup>National Cancer Institute, Frederick, MD, USA

**Background:** Blockade of the programmed cell death protein-1 (PD-1) pathway can reverse HIV latency, can potentiate virus-specific CD8 T cell responses, and has been associated with favorable outcome in some cases of central nervous system (CNS) infection. The effects of PD-1 blockade on CNS reservoirs for HIV are under study in clinical trial NCT03239899. We evaluated HIV-infected CD4 T cell reservoirs in blood in participants from this trial.

**Methods:** People with HIV on ART and with CD4 counts >350 cells/μL received one infusion of 200 mg pembrolizumab, a monoclonal antibody against PD-1. PBMC were collected at baseline and at 3 and 24 weeks post-infusion. Control participants who had not received pembrolizumab were also studied. CD4 T cells in PBMC were FACS-sorted into naïve, central/transitional memory (CTM), and effector memory (EM) subsets. HIV DNA in sorted cells was quantified by limiting dilution PCR of a portion of env. PCR products were Sanger sequenced. HIV RNA was quantified by qRT-PCR. Cell gene expression patterns were determined by mRNA-Seq. Paired integration site analysis and near-full length sequencing was performed by multiple-displacement amplification and single-genome sequencing. Intact HIV proviruses in total CD4 T cells were enumerated with intact proviral DNA assay.

**Results:** Pembrolizumab infusion and 24 weeks of follow-up were completed for six participants. Changes in sorted cell HIV DNA and RNA over time were similar in pembrolizumab-treated and control groups. However, a shift in distribution of HIV-infected cells to the EM subset and a reduced genetic diversity of HIV DNA sequences were observed after pembrolizumab. These were associated with lower levels of T cell activation signaling gene transcripts and with expansion of a small number of HIV-infected cell clones. In one participant, one clone expanded to account for ~1% of all circulating CD4 T cells post-infusion. This clone harbored a provirus with a deletion in the major splice donor site. Intact proviruses were infrequent in both pembrolizumab-treated and control participants, with no consistent change in frequency over time in either group.

**Conclusion:** PD-1 blockade was associated with perturbations in the HIV-infected CD4 T cell pool including a shift to an EM phenotype and further expansion of some infected cell clones. Further investigation of intact proviruses in T cell clones following checkpoint inhibitor administration will help clarify the net effect of these agents in HIV cure strategies.



**Figure 1.** HIV-infected CD4 T cell clonal expansion after PD-1 blockade, without clear increases in intact reservoir size. **A)** Expansion of EM cells harboring a defective provirus integrated in ARHGAP26 (chr5) after PD-1 blockade in one participant. **B)** Quantification of intact proviruses in pembrolizumab-treated and control participants by IPDA.

**300 THE PERIPHERAL CD4+ T-CELL RESERVOIR ATLAS IN cART-TREATED HIV-INFECTED INDIVIDUALS**

Cristina Gálvez<sup>1</sup>, Judith Grau-Expósito<sup>2</sup>, Victor Urrea<sup>1</sup>, Maria José Buzón<sup>2</sup>, Javier Martínez-Picado<sup>1</sup>

<sup>1</sup>IrsiCaixa Institute for AIDS Research, Badalona, Spain, <sup>2</sup>Hospital Universitari de la Vall d'Hebron, Barcelona, Spain

**Background:** The knowledge of the mechanisms that govern the persistence of the distinct subpopulations of CD4+ T cells harboring HIV could help to design new therapies to cure HIV. Here, we evaluate the distribution of the HIV reservoir in 12 different CD4+ T cell subpopulations in peripheral blood and its relationship with immune activation, cell proliferation and cytokine profiling.

**Methods:** A 500ml blood drawn was obtained from 14 HIV-infected individuals under cART from Hospital Vall d'Hebrón. From PBMCs, we isolated total CD4+ T cells, TN, TSCM, TCM, TTM, TEM, TFH, TCD20, TCD32, and TCD2high cells by cell sorting, and activated and resting CD4+ T cells using magnetic beads. Total HIV-DNA and intact provirus were measured in all cell populations by ddPCR. The expression of HIV-RNA transcripts was measured in 10 cell populations (CD4+, TN, TSCM, TCM, TTM, TEM, TFH, TCD20, TCD32, TCD2high) by the RNA FISH/flow assay, and by the cell-associated HIV-RNA assay in total CD4+ T cells. Activation (CD69, HLA-DR and CD38), proliferation (Ki-67) and exhaustion (PD-1) cell markers were studied by flow cytometry. Ultrasensitive viral load (uVL) and cytokines (Luminex) were measured in all plasma samples.

**Results:** Total HIV-DNA showed that the most infected cell populations had a memory phenotype (TTM, TEM, TCD2high, TCD20, and TCM), harboring all the cell populations studied intact provirus. Moreover, TCD32, TFH, TTM and

TCD20 were the main cell populations supporting HIV-1 transcription. We found significant positive correlations between HIV-DNA and HIV-RNA expression in 8/10 cell populations measured by ca-HIV-RNA; TCD20 and TCD32 measured by RNA FISH/Flow; and TEM, TFH and TSCM measured by usVL. Phenotypic analysis by flow cytometry showed that cell populations with higher provirus were, in general, more exhausted and less activated (TM, TEM, TCD2high); and that cell populations with higher levels of proliferation had also a high HIV-RNA expression (TFH, TCD32). HIV-DNA in TCM cells were negatively related with the plasma cytokines IFN $\gamma$ , TNF and IL17a/CTLA8, being the latest significantly correlated with HIV-DNA in 7/10 populations studied.

**Conclusion:** Upon simultaneous analysis of 12 CD4+ T subpopulations in peripheral blood, we found that the different cells that composed the persistent HIV reservoir during cART are linked to different activation and inflammation profiles, demonstrating the high heterogeneity of the HIV reservoir. This study provides new knowledge to target specific cell reservoirs.

### 301 HIV PERSISTS PREFERENTIALLY IN MEMORY CD4+ T CELLS CO-EXPRESSING PD1 AND CTLA4

**Thomas A. Rasmussen**<sup>1</sup>, Jennifer Zerbato<sup>1</sup>, Ajantha Rhodes<sup>1</sup>, Ashanti Dantanarayana<sup>1</sup>, James McMahon<sup>2</sup>, Jillian S. Lau<sup>2</sup>, Wendy Brown<sup>3</sup>, Rebecca Hoh<sup>4</sup>, Nicolas Chomont<sup>5</sup>, Jeffrey Milush<sup>4</sup>, Sarah Palmer<sup>6</sup>, Steven G. Deeks<sup>4</sup>, Vanessa Evans<sup>1</sup>, Sharon Lewin<sup>1</sup>, for the HIV-PRADA Study Group

<sup>1</sup>Doherty Institute for Infection and Immunity, Melbourne, Australia, <sup>2</sup>The Alfred Hospital, Melbourne, Australia, <sup>3</sup>Monash University, Melbourne, Australia, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA, <sup>5</sup>Centre Hospitalier de l'Université de Montreal, Montreal, Canada, <sup>6</sup>University of Sydney, Westmead, Australia

**Background:** Identifying cellular subsets that preferentially harbour HIV is important for curative strategies. We aimed to address the role of the immune checkpoints, programmed cell death 1 (PD1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4) for HIV persistence on ART.

**Methods:** We collected peripheral blood mononuclear cells (PBMCs) and lymph node (LN) mononuclear cells by performing leukapheresis and LN biopsies in people with HIV (PWH) on suppressive ART. Memory CD4+ T cells were sorted into four subsets based on their expression of PD1 and CTLA4 to obtain: double-positive (PD1+CTLA4+), PD1 single positive (PD1+CTLA4-), CTLA4 single positive (PD1-CTLA4+) and double-negative (PD1-CTLA4-) cells. Within each sorted subset from blood and LN we quantified total HIV DNA and cell-associated unspliced HIV RNA (CA-US HIV RNA) and also performed the tat/rev limiting dilution assay (TILDA) to quantify the frequency of cells with inducible multiply-spliced HIV RNA.

**Results:** We enrolled 21 PWH with 4.2-14.1 years of ART-mediated viral suppression. We obtained paired LN biopsies and leukapheresis samples in 8 participants and leukapheresis only in 13 participants. The frequency of memory CD4+ T cells co-expressing PD1 and CTLA4 was higher in LN tissue compared to blood whereas double-negative cells were more frequent in blood. We found a significant enrichment of total HIV DNA in blood memory CD4+ T cells co-expressing PD1 and CTLA4 with a median 1.8-fold (IQR 1.1-2.5, P=0.018) higher level of HIV DNA when compared to their double-negative counterpart. This enrichment was not seen in LN cells. The frequency of cells containing HIV DNA within most PD1/CTLA4 subsets in both blood and LN correlated with higher CD8+ T cell counts and percentages at study entry. Despite their enrichment for total HIV DNA, a lower proportion of double-positive memory CD4+ T cells in blood produced multiply spliced HIV RNA upon PMA/ionomycin stimulation. There was no difference across PD1/CTLA4 subsets in the level of CA-US HIV RNA in blood or LN.

**Conclusion:** The frequency of HIV-infected cells was moderately higher in blood memory CD4+ T cells co-expressing PD1 and CTLA4 but this enrichment was not seen in LN. Double-positive memory CD4+ T cells from blood had a lower frequency of inducible virus, potentially indicating these cells are characterised by their negative signalling and a limited susceptibility to induction of latent HIV.

### 302 SINGLE-CELL TRANSCRIPTOMIC T-CELL STATES OF A RESERVOIR-MARKING HU-MOUSE MODEL

**Namita Satija**<sup>1</sup>, Foramben Patel<sup>1</sup>, Manav K. Kapoor<sup>1</sup>, Annalena Laporte<sup>1</sup>, Zichen Wang<sup>1</sup>, Kenneth Law<sup>1</sup>, Anthony M. Esposito<sup>2</sup>, Hiroshi Mori<sup>3</sup>, Kimaada Allette<sup>1</sup>, Kristin Beaumont<sup>1</sup>, Robert Sebra<sup>1</sup>, Benjamin K. Chen<sup>1</sup>  
<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>2</sup>New Jersey City University, Jersey City, NJ, USA, <sup>3</sup>Aaron Diamond AIDS Research Center, New York, NY, USA

**Background:** Human immunodeficiency virus (HIV-1) causes a chronic infection in which the virus persists in a latent state in patient CD4 T cells integrated into the host genome. This pool of virus persists during effective antiretroviral therapy (ART) and represents the major barrier to cure. Our ability to study the HIV-1 reservoir is limited because current model systems requires activation of latently infected cells to enumerate or characterize them. The activation of the cells disturbs the unique characteristics that maintain latency.

**Methods:** We have developed a novel HIV-1-induced lineage tracing (HILT) humanized mouse model that can irreversibly report if a CD4 T cell was ever infected by HIV-1. The system utilizes a genetically encoded, cre-lox activated fluorescent protein switch in which a cre-expressing virus irreversibly changes the phenotype of target cells that are transduced as stem cells to express the cre-activated switch. We validate the system and examine HILT-marked cells using single cell RNA sequencing to provide transcriptional profiles of HIV-infected cells before and after antiretroviral therapy (ART).

**Results:** The HILT model recapitulates features of HIV-1 pathogenesis including sustained viremia, CD4 cell depletion, response to ART and re-emergence of virus following treatment interruption. Using high throughput single cell RNA sequencing (scRNAseq) we have obtained transcriptional profiles of acutely infected and persistently infected CD4 T cells following the initiation of ART. Splenic CD4 T cells are organized in 7-8 major transcriptionally defined clusters and acutely infected and persistently HIV-1 infected cells are distributed in diverse subsets indicating that HIV infects and persists in cells with diverse transcriptional states. During acute infection HIV gene expression is detectable, whereas following ART, viral mRNA was not detected in cells.

**Conclusion:** HIV infected cells are interspersed in diverse clusters of CD4 T cells, both before and after ART. HIV-associated differential gene expression analysis reveal pathways that with known interactions with HIV transcriptional regulation. The approach of marking of HIV infected cells, combined with a single cell transcriptional analysis of HIV infection underscores the transcriptomic diversity within HIV reservoir and reveals gene regulation pathways potentially associated with HIV persistence.

### 303 SINGLE-CELL RNAflow-FISH REVEALS TRANSCRIPTIONAL DIVERSITY FOLLOWING LATENCY REVERSAL

**Gérémy Sannier**<sup>1</sup>, Mathieu Dubé<sup>1</sup>, Caroline Dufour<sup>1</sup>, Nathalie Brassard<sup>1</sup>, Gloria G. Delgado<sup>1</sup>, Amy Baxter<sup>2</sup>, Julia Niessi<sup>1</sup>, Roxanne Charlebois<sup>1</sup>, Amélie Pagliuzza<sup>1</sup>, Rémi Fromentin<sup>1</sup>, Jean-Pierre Routy<sup>3</sup>, Nicolas Chomont<sup>1</sup>, Daniel E. Kaufmann<sup>1</sup>  
<sup>1</sup>Centre de Recherche du CHUM, Montreal, Canada, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>McGill University Health Centre, Montreal, Canada

**Background:** "Shock and kill" cure strategies rely on the efficient induction of HIV transcription in latently infected cells by latency reversing agents (LRAs). Since latently infected cells are highly heterogeneous in vivo, investigating the activity of latency reversal agents at the single-cell level in clinical samples is crucial.

**Methods:** We developed a novel single-cell multiplexed RNA flow cytometric fluorescent in situ hybridization (RNAflow-FISH) assay for co-detection of viral RNA (vRNA: gagRNA, nefRNA and HIV exons) and p24 protein. We applied this approach to PBMCs from 11 ART-suppressed people living with HIV. We examined HIV transcription and translation induced by PMA/Ionomycin, HDAC inhibitors (panobinostat, vorinostat; HDACi), and PKC agonists (bryostat, PEP005; PKCa).

**Results:** We detected a median of 115 vRNA+ cells/10<sup>6</sup> CD4+ T cells upon PMA/Ionomycin stimulation, a frequency only 6.8-fold lower than integrated HIV DNA (median 783). Only a small fraction of these cells produced the HIV protein p24 (median 3.9%), which all co-expressed gag and nef RNA. Reactivated cells were dominated by transcriptionally heterogeneous vRNA+p24- cells: gag+nef- (median 47%) > gag-nef+ (median 30%) > gag+nef+ (median 12%). PEP005 and panobinostat resulted in robust latency reversal (median of 54 and 55 vRNA+ cells/10<sup>6</sup> CD4+ T cells, respectively). While PEP005 recapitulated the profile obtained with PMA/ionomycin, panobinostat induced an homogenous gag+nef-p24- population (median of

88% of vRNA+) with few nef RNA. These profiles were consistent within LRA classes. Combining PEP005 and panobinostat boosted reactivation at a level surpassing PMA/ionomycin (median 240 vRNA+ cells/10<sup>6</sup> CD4+ T cells) with a profile similar to panobinostat, without p24 expression. We performed single-cell nested near full-length PCR on index sorted PMA/ionomycin-stimulated viral reservoirs to relate viral integrity to virus transcription. Highly deleted proviruses were enriched in gag-nef+p24- and gag-nef-p24- populations. Both gag+nef+p24- and p24+ populations harbored potentially intact proviruses. **Conclusion:** We identified distinct single-cell patterns of viral reactivation upon stimulation by latency reversal agents in clinical samples. Dissociated expression of structural and regulatory genes was frequent, and differences between LRA classes were observed. Regardless of the agent tested, only a minority of the cells in which HIV transcription was efficiently induced produced detectable levels of the HIV protein p24.

**304 RESTING AND ACTIVATED CD4+ T CELLS BOTH HAVE SILENT AND ACTIVE HIV PROVIRUSES IN VIVO**

**Jennifer L. Groebner**<sup>1</sup>, Liliana Pérez<sup>2</sup>, Rachel Sklutuis<sup>1</sup>, Michael J. Bale<sup>1</sup>, Wei Shao<sup>3</sup>, Ann Wiegand<sup>1</sup>, Steven G. Deeks<sup>1</sup>, Deborah McMahon<sup>5</sup>, Joseph J. Eron<sup>6</sup>, Rajesh T. Gandhi<sup>7</sup>, Frank Maldarelli<sup>1</sup>, John M. Coffin<sup>8</sup>, John W. Mellors<sup>5</sup>, Eli A. Boritz<sup>2</sup>, Mary F. Kearney<sup>1</sup>  
<sup>1</sup>National Cancer Institute, Frederick, MD, USA, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>3</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA, <sup>5</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>6</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>7</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>8</sup>Tufts University, Boston, MA, USA

**Background:** Resting CD4+ T cells are thought to harbor transcriptionally-silent proviruses. We previously reported that only a small fraction of the cells in infected cell clones that persist on ART have proviruses expressing unspliced (us) HIV RNA (median 5%, range <1-65%). We evaluated whether these transcriptionally active HIV proviruses are preferentially found in activated rather than resting CD4+ T cells.

**Methods:** Leukopaks were obtained from donors in the ACTG A5341s study, the SCOPE cohort, and NIH trial protocols 97-I-0082 and 08-I-0221. Donors had been on effective ART for a median of 9 years (range 6.7-19.0 years). PBMC were FACS sorted on HLA-DR expression and collected in aliquots near an endpoint for infected cells. The number of infected cells was estimated before sorting from measurements of HIV DNA in total PBMC and from the percent CD4+ T cells. The samples were tested using our cell-associated RNA and DNA single-genome sequencing (CARD-SGS) assay to determine the number of infected cells, the fraction with us-HIV RNA, and the levels and sequences of HIV RNA and DNA in single cells.

**Results:** We assayed levels of us-HIV RNA in a median of 146,000 single HLA-DR+ and 1,052,500 single HLA-DR- CD4+ T cells from 6 participants. The frequencies of HIV-infected DR- and DR+ T cells were not different (median 0.1% in each subset). A median of 6% (range 4-9%) of the DR- cells and 4% (range 2-5%) of the DR+ cells expressed us-HIV RNA at the time of sample collection. Levels of us-HIV RNA in single DR- and DR+ cells were low (median 1.3 vs. 1.4 RNA copies/cell respectively). The HIV DNA sequences in the two subsets did not show differences in genetic diversity (average pairwise difference 1.9% vs. 1.7%) and were not genetically compartmentalized across the subsets (panmixia=0.06). In a cell clone with a replication-competent provirus that consisted of both DR+ and DR- cells, the fraction of cells with us-HIV RNA was 7% in both subsets.

**Conclusion:** Our finding that transcriptionally active proviruses are present at a similar frequency in HLA-DR- and HLA-DR+ T cells in people with HIV on ART supports the idea that the latent reservoir is not only in "resting" cells. The very low levels of HIV RNA in both HLA-DR- and HLA-DR+ T cell subsets also implies that cellular activation marker expression is not a reliable indicator of proviral activation in vivo.

**305 COMPLETED GENOME-INTACT UNSPLICED HIV TRANSCRIPTS ARE RARE IN EX VIVO CD4+ CELLS**

**Nancy Francoeur**<sup>1</sup>, Yanqin Ren<sup>2</sup>, Pragma Khadka<sup>2</sup>, Winiffer D. Conce Alberto<sup>2</sup>, Gintaras Deikus<sup>1</sup>, Erika Benko<sup>3</sup>, Colin Kovacs<sup>3</sup>, Ales Varabyou<sup>4</sup>, Mihaela Percea<sup>5</sup>, Yang-Hui Yeh<sup>6</sup>, Ya-Chi Ho<sup>6</sup>, Robert Sebra<sup>1</sup>, R. Brad Jones<sup>2</sup>, Melissa Smith<sup>7</sup>, Guinevere Q. Lee<sup>2</sup>

<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>2</sup>Weill Cornell Medicine, New York, NY, USA, <sup>3</sup>Maple Leaf Medical Clinic, Toronto, Canada, <sup>4</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>5</sup>Jagiellonian University, Kraków, Poland, <sup>6</sup>Yale University, New Haven, CT, USA, <sup>7</sup>University of Louisville, Louisville, KY, USA

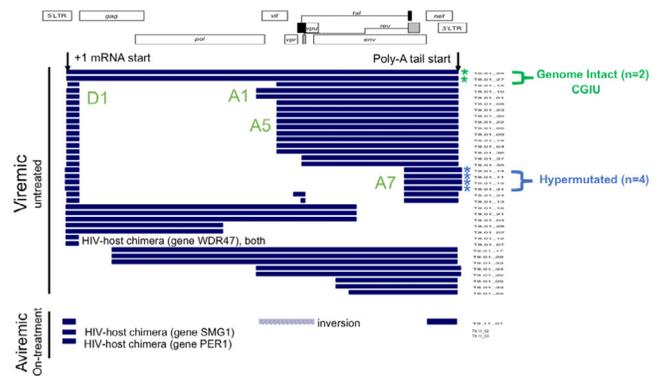
**Background:** During virologic rebound, HIV-infected cells must produce 5' to 3' completed, genome-intact and unspliced (CGIU) viral transcripts for packaging into new virions. Conventional methods to study HIV transcription are unable to obtain genome-intactness information. Here, we present a novel high-fidelity long-read sequencing method, TranSeq, and profiled HIV transcriptomes in clinically-derived CD4+ cells with emphasis on CGIU transcripts.

**Methods:** CD4+ cells were enriched from total PBMCs. Poly-adenylated RNA was extracted and subjected to TranSeq using PacBio Sequel II single molecule real-time long read sequencing at an average of 3 million reads per sample. Resulting reads were analyzed using an in-house bioinformatics pipeline. A completed HIV transcript was defined as possessing +1mRNA, 3'LTR end site, and a poly-adenylated tail.

**Results:** Human cell line 8E5/LAV with an integrated and defective HIV genome was used for benchmarking. We sampled 940 cells and observed 2882/12858 (22%) completed, unspliced transcripts. Next, we examined unstimulated CD4+ cells from two persons with viral load 96125 (untreated viremic) and 92 copies/mL (persistent low-level viremic). We sampled ~100,000 CD4+ cells each and detected 37 and 0 HIV transcripts respectively (Figure 1). Despite the highly viremic state in the first individual, only 2, 13 and 2 transcripts were completed genome-intact unspliced (CGIU), singly-spliced and doubly-spliced respectively. APOBEC-associated hypermutations were present in 4/37 (11%). HIV-human splice chimeras were in 2/37 (5%). Then, we examined 100,000-700,000 unstimulated CD4+ cells from five treated and virologically suppressed individuals: Only one was positive for three copies of HIV transcripts: One displayed defective splicing with an internal inversion, whereas two spliced from splice donor 1 into known splice acceptor sites in human genes SMG1 and PER1 (Figure 1). In this individual, ex vivo stimulation by PMA/ionomycin or CD3/CD28 increased HIV transcripts detection by 375- and 20-fold respectively.

**Conclusion:** Our results suggest CGIU transcripts were rare. Even during uncontrolled viremia, cell-associated CGIU transcripts only made up 2/37 (5%) of the HIV transcriptome, and were undetectable in the low-level viremic and virologically suppressed individuals. Future studies will increase sampling-depth and explore time- and dosage-dependent effects of latency reversing agents on CGIU transcripts production.

**Figure 1. High-fidelity HIV transcriptome sequence profiling suggests that completed genome-intact unspliced CGIU transcripts (in green) are rare.**



### 306 EXPRESSION OF CD32 IN HIV-RESERVOIR CELLS CONFERS RESISTANCE TO NATURAL KILLER CELLS

Antonio Astorga Gamaza<sup>1</sup>, Judith Grau-Expósito<sup>1</sup>, Joaquin Burgos-Cibrian<sup>2</sup>, Jordi Navarro<sup>2</sup>, Adrià Curran<sup>2</sup>, Berta Raventós<sup>1</sup>, Ariadna Torrella<sup>1</sup>, Bibiana Planas<sup>1</sup>, Paula Suanzes<sup>2</sup>, Vicenç Falcó<sup>2</sup>, Meritxell Genescà<sup>1</sup>, Maria José Buzón<sup>1</sup>  
<sup>1</sup>Vall d'Hebron Research Institute, Barcelona, Spain, <sup>2</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain

**Background:** HIV establishes a persistent infection in cell reservoirs which are not susceptible to current antiretroviral therapy (ART). The expression of the Fcγ receptor CD32 in infected cells has been identified as a marker of the active cell reservoir that persist during ART, but the mechanism by which these cells are maintained and evade the action of the immune system is currently unknown.

**Methods:** Antibody-dependent cell cytotoxicity (ADCC) and natural cytotoxicity (NC) NK functional responses were evaluated by flow cytometry in different subpopulations of CD4+ T cells after peptide-loading (n=30), ex-vivo infection (n=14) and viral reactivation from latency (n=6). Protein-defective viruses were used to elucidate the contribution of HIV to CD32 upregulation. Binding of HIV-specific antibodies, cell proliferation in response to immune complexes (IC) and expression of NK-ligands HLA-E, MICA/B, CD155 and ULBP after ADCC and NC, were measured by flow cytometry. The viral reservoir was assessed by quantification of total HIV-DNA and caHIV-RNA by qPCR in CD4+ T cells from ART-suppressed patients. Statistical comparisons were performed using Wilcoxon matched-pairs signed rank test, Mann-Whitney test, ANOVA Friedman test, and Spearman correlations, when appropriate.

**Results:** CD4+ T cells expressing CD32 were highly resistant to ADCC after peptide-loading (ANOVA p=0.0001) (Figure 1), and ex-vivo infection (median % 19.6 vs. 35.8 for TCD32+ and TCD32-, p<0.01). This observation was particularly significant in ART-suppressed patients compared with elite controllers and healthy donors (median % 0.0, 34.8 and 45.0, for ART, EC and HD, p<0.01). Upregulation of CD32 was facilitated by the viral protein Nef (p<0.0001), decreased HIV-specific antibody binding (p<0.05), and conferred cell proliferation potential upon IC engagement (mean %Ki67 9.8 vs. 20.5 for basal vs. plasma HIV+, p<0.01). NK-resistant CD32-expressing cells expressed higher levels of HLA-E (median % 22.2 and 11.0, for TCD32+ and TCD32-, p<0.0001), but the administration of anti-HLA-E blocking antibodies, IFN-α or IL-15 did not reverse immune resistance. Furthermore, latently HIV-infected cells expressing CD32 upon viral reactivation resisted NK-killing (p<0.05) and an inverse correlation was observed between ADCC-killing and total HIV-DNA reservoir size (p=0.02).

**Conclusion:** We report a novel mechanism of viral evasion to NK-immune responses through the upregulation of CD32, which might represent a new obstacle to fully eliminate HIV.

Figure 1

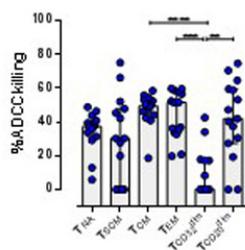


Figure 1. Susceptibility of different cell subpopulations that compose the HIV-reservoir to NK-mediated killing by ADCC in samples from ART-suppressed patients. The intrinsic cell susceptibility to ADCC was measured in Naive (T<sub>Naive</sub>), Stem Cell Memory (T<sub>SCM</sub>), Central Memory (T<sub>CM</sub>), Effector Memory (T<sub>EM</sub>), T<sub>CD32</sub><sup>+</sup> and T<sub>CD32</sub><sup>-</sup> subsets. Statistical comparisons were performed using ANOVA Friedman test. Median with interquartile range is shown.

### 307 PROFILING THE PROVIRAL LANDSCAPE IN TISSUES FROM ART-TREATED INDIVIDUALS

Weiwei Sun<sup>1</sup>, Yelizaveta Rassadkina<sup>1</sup>, Aurelie Schaison<sup>1</sup>, Ce Gao<sup>1</sup>, Sarah I. Collens<sup>2</sup>, Isaac H. Solomon<sup>3</sup>, Shibani Mukerji<sup>2</sup>, Xu Yu<sup>1</sup>, Mathias Lichterfeld<sup>3</sup>  
<sup>1</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>2</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>3</sup>Brigham and Women's Hospital, Boston, MA, USA

**Background:** HIV reservoir cells that circulate in blood have been well characterized, but little is known about the dissemination of HIV-1-infected cells

across multiple anatomical tissues, especially the central nervous system (CNS). Here, we performed single-genome near-full-length proviral sequencing to evaluate the proviral landscape in multiple tissues from 2 ART-treated patients.

**Methods:** Frozen tissues derived from 2 ART-treated individuals, were sampled during autopsy. Genomic DNA was extracted, and HIV-1 DNA levels were initially quantified using the intact proviral DNA assay (IPDA), followed by single-genome near-full-length proviral sequencing.

**Results:** In patient 1, 577 HIV-1 sequences were detected in 14 different tissues from 754.77 million cells. Most of these proviruses were defective, and only a small fraction (4.5%, n=26) were intact, located in lymph node (n=18), spleen (n=3), colon (n=2), and kidney (n=3). The number of HIV copies varied from 0.02 to 6.24/million cells. The frequency of HIV sequences was highest in lymph node (6.24 total copies/million cells; 0.62 intact proviruses/million cells), followed by colon, spleen, and kidney. Four different sections of CNS were analyzed (occipital cortex, frontal cortex, basal ganglia and thalamus), but only 9 defective HIV sequences and no intact sequences were retrieved from 162.85 million cells. Two clones of intact proviruses were observed, one exclusively located in lymph node and the other disseminated across lymph node, spleen, and kidney. Ten large clones of defective proviruses were also noticed, which were broadly distributed across lymph node, spleen, the CNS, the genitourinary system, and the gastrointestinal system. In patient 2, 5 different CNS sections were analyzed, with isolation of a total of 36 HIV sequences from 147.49 million cells. Only 1 intact sequence was detected in the basal ganglia. The number of HIV copies varied from 0.10 to 0.47/million cells. Basal ganglia had the highest frequencies of HIV sequences, relative to frontal cortex, ventricle, occipital cortex and thalamus. Three clones of defective proviruses were observed across multiple CNS sections.

**Conclusion:** Lymph node represents a tissue hotspot for viral persistence, while the CNS does not seem to be a major site for persistence of intact proviruses. Multi-compartment dissemination of clonal intact and defective proviruses occurred across multiple anatomical tissues, arguing against compartmentalization of HIV reservoir cells in specific tissue types.

### 308 HIV-INFECTED LYMPH NODE MIGRATORY DENDRITIC CELLS PERSIST IN ART-TREATED INDIVIDUALS

Riddhima Banga<sup>1</sup>, Francesco A. Procopio<sup>1</sup>, Erica Lana<sup>2</sup>, Annamaria Kauzlaric<sup>1</sup>, Olivia M. Monje<sup>2</sup>, Craig Fenwick<sup>2</sup>, Matthias Cavassini<sup>2</sup>, Jean-Marc Corpataux<sup>2</sup>, Mauro Delorenzi<sup>1</sup>, Giuseppe Pantaleo<sup>2</sup>, Matthieu Perreau<sup>2</sup>  
<sup>1</sup>University of Lausanne, Lausanne, Switzerland, <sup>2</sup>Lausanne University Hospital, Lausanne, Switzerland

**Background:** While pioneering studies demonstrated that HIV replication and spreading mainly occur in lymphoid tissues, the identification of specific cell subsets harboring replication competent virus in lymphoid tissues has long time been neglected. In this context, we and others have recently shown that gut memory CD4 T cells, lymph node (LN) T follicular helper cells and tissue macrophages represent major HIV/SIV tissue reservoirs. LN dendritic cells (DCs) are endowed with an exceptional T-cell stimulatory potential and can either migrate from the periphery to the draining lymph node (migratory DCs) or locate in the LN for their entire life span (resident DCs). On the basis of these unique properties, long-term persistence of LN DCs infected with replication competent virus may represent the initial trigger of viral rebound post ART interruption and may therefore represent a major obstacle to HIV cure.

**Methods:** We therefore comprehensively assessed major virological parameters associated with HIV persistence in ex vivo isolated LN migratory and resident DCs isolated from viremic (N=3) and aviremic ART treated HIV-infected subjects (N=7).

**Results:** LN migratory DCs harbored a much higher propensity for HIV infection in vitro than resident DCs (P<0.05) and supported HIV production, which was associated with significantly lower levels of SAMHD1 transcripts (P<0.05). Interestingly, LN migratory DCs isolated directly ex vivo from viremic individuals harbored higher frequencies of cells harboring integrated HIV DNA, unspliced gag and multi-spliced tat-rev HIV RNA as compared to resident DCs. In addition, LN migratory DCs supported higher reactivation of HIV production (in the absence of CD4) and replication (in the presence of CD4) in vitro as compared to resident DCs. Interestingly, HIV-infected LN migratory DCs were still detectable in treated HIV-infected individuals and were able to support much higher levels of HIV production and replication when co-cultured with target CD4 T cells in vitro as compared to LN resident DCs (P<0.05).

**Conclusion:** The present study underscored a yet underestimated role of LN DCs in HIV persistence and may therefore highlight the need to adapt the currently explored experimental strategies aiming at purging viral reservoirs.

### 309 LONGITUDINAL DYNAMICS OF INTACT PROVIRAL HIV-1 DNA IN POSTTREATMENT CONTROLLERS

**Xiaodong Lian**<sup>1</sup>, Kyra W. Seiger<sup>1</sup>, Gregory T. Gladkov<sup>1</sup>, Joshua Chevalier<sup>1</sup>, Kevin B. Einkauf<sup>1</sup>, Jane E. Blackmer<sup>1</sup>, Chenyang Jiang<sup>1</sup>, Eric S. Rosenberg<sup>2</sup>, Ce Gao<sup>1</sup>, Xu Yu<sup>1</sup>, Tae-Wook Chun<sup>3</sup>, Mathias Lichterfeld<sup>1</sup>

<sup>1</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>2</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>3</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

**Background:** In HIV-1 infected individuals, discontinuation of antiretroviral combination therapy (cART) typically results in rapid viral rebound. However, a small number of individuals, termed post-treatment controllers (PTCs), exhibit sustained virologic suppression for months or years following cART interruption. The dynamics and evolution of the proviral reservoirs of these individuals are largely unknown.

**Methods:** Samples from 3 PTCs, who maintained undetectable or low viremia for up to 18 years after cART cessation, were longitudinally collected. Genomic DNA was diluted to single proviral genomes, followed by full-length individual proviral sequencing (FLIP-Seq) or matched integration site and proviral sequencing (MIP-Seq). Near full-length sequencing of single-genome HIV-1 plasma RNA was also performed.

**Results:** In total, 2633 individual proviral genomes were obtained. 59 integration sites of intact proviruses were identified, of which 47 were located at unique chromosomal positions. At baseline prior to ART interruption, the relative frequencies of total and intact proviruses in PTCs were comparable to a background population of ART-treated individuals, with 23% (n=14) of intact proviruses being part of expanded clones. Notably, these clonally-expanded intact proviruses were frequently located in non-genic, centromeric satellite DNA (n=11, 79%); in contrast, non-clonal intact proviruses at baseline were preferentially located in genic chromosomal positions (n=22, 73%). Intact proviruses in expanded clones located in centromeric satellite DNA were repeatedly detected at multiple follow-up time points up to 14 years apart, while non-clonal proviruses integrated in genic chromosomal positions were selectively eliminated over time. 4-14 years after treatment interruption, 72-100% of all intact proviral sequences were clonally expanded and integrated in non-genic satellite DNA. In one PTC with plasma viral blips, we were able to obtain 12 near full-length plasma viral sequences, which showed close phylogenetic associations to non-clonal intact proviral sequences.

**Conclusion:** PTC display a unique integration site landscape with enrichment of intact proviruses in centromeric satellite DNA associated with deep latency, as previously shown for elite controllers. These data suggest that EC and PTC share similar underlying immune selection mechanisms that preferentially eliminate intact proviruses in chromosomal regions susceptible to reactivation signals, while intact proviruses in deep latency persist.

### 310 CELL-FREE DNA PREDICTS HIV REBOUND TIMING FOLLOWING ANTIRETROVIRAL THERAPY CESSATION

**Zain Y. Dossani**<sup>1</sup>, Karla Medina<sup>1</sup>, Erika Marques de Menezes<sup>1</sup>, Anna Sellas<sup>1</sup>, Xutao Deng<sup>1</sup>, Reuben Thomas<sup>2</sup>, Katherine Pollard<sup>3</sup>, Philip Norris<sup>1</sup>, Clara Di Germanio<sup>1</sup>, Nadia Roan<sup>2</sup>, Warner Greene<sup>2</sup>, Ole Søgaard<sup>3</sup>, Martin Tolstrup<sup>3</sup>, Satish Pillai<sup>1</sup>

<sup>1</sup>Vitalant Research Institute, San Francisco, CA, USA, <sup>2</sup>Gladstone Institutes, San Francisco, CA, USA, <sup>3</sup>Aarhus University Hospital, Aarhus, Denmark

**Background:** The development of HIV cure strategies depends on our capacity to predict HIV rebound when antiretroviral therapy (ART) is stopped. Here, we applied a systems profiling approach to the analytical treatment interruption (ATI) framework, to identify circulating plasma factors that enable non-invasive prediction of viral rebound kinetics post-ART cessation.

**Methods:** Plasma samples were retrospectively collected from three Danish ATI cohorts (CLEAR, TEACH, REDUC, N=34 participants). The following assays were applied to pre-ATI (baseline) samples: 1) Cell-free DNA (cfDNA) abundance and fragment size were characterized using fluorimetry (Qubit) and capillary electrophoresis (Agilent BioAnalyzer). 2) Extracellular vesicle (EV) abundance and composition were analyzed using nanoparticle tracking analysis (Malvern NanoSight) and flow cytometry-based measurement of 25 surface protein markers (BD LSR II). 3) The titer and antigen specificities of anti-HIV antibodies were measured by recombinant antigen binding (Ortho Vitros) and luciferase

immunoprecipitation systems (LIPS) assays, respectively. 4) Circulating levels of 28 cytokines were measured by immunoassay (Luminex). Pearson correlations between biomarker levels and time to HIV rebound (days until viral load >50 copies/mL) and false discovery rate corrections were calculated using scipy and statsmodels Python libraries in custom Python scripts.

**Results:** Five features exhibited significant correlations with viral rebound timing after FDR correction. cfDNA abundance exhibited the strongest (positive) correlation with time until rebound (FDR<0.03; R<sup>2</sup>=0.62). The four remaining predictive features were EV surface proteins; frequencies of EVs expressing the ecto-5'-nucleotidase CD73, glial fibrillary acidic protein (GFAP), fractalkine receptor CX3CR1, and major histocompatibility complex (MHC) class II were positively correlated with time until rebound (FDR<0.05).

**Conclusion:** Our systems approach revealed that elevated circulating cfDNA abundance and elevated expression of select immunomodulatory proteins on the EV surface are associated with delayed HIV rebound following ART cessation. These biomarkers can be conveniently and cost-effectively measured using small volumes of plasma, reinforcing their prognostic value. Our findings warrant confirmation in additional ATI cohorts. In addition, deciphering the mechanisms linking these predictive biomarkers to viral reactivation and immune control may lead to novel HIV cure approaches.

### 311 IMMUNE MARKERS AND TO TIME TO REBOUND DURING HIV TREATMENT INTERRUPTION IN ACTG A5345

**Bernard Macatangay**<sup>1</sup>, Jonathan Li<sup>2</sup>, Evgenia Aga<sup>3</sup>, Ronald J. Bosch<sup>3</sup>, Jennifer Kinslow<sup>4</sup>, Mark Plinkton<sup>5</sup>, Lynsay MacLaren Ehui<sup>6</sup>, Eugene Kroon<sup>7</sup>, Jintanat Ananworanich<sup>8</sup>, Robert Coombs<sup>9</sup>, John W. Mellors<sup>1</sup>, Steven G. Deeks<sup>10</sup>, Rajesh T. Gandhi<sup>11</sup>, Davey M. Smith<sup>12</sup>, Alan Landay<sup>13</sup>

<sup>1</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>2</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>3</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>4</sup>Rush University, Chicago, IL, USA, <sup>5</sup>Vanderbilt University, Nashville, TN, USA, <sup>6</sup>Whitman-Walker Health, Washington, DC, USA, <sup>7</sup>Thai Red Cross AIDS Research Centre, Bangkok, Thailand, <sup>8</sup>Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands, <sup>9</sup>University of Washington, Seattle, WA, USA, <sup>10</sup>University of California San Francisco, San Francisco, CA, USA, <sup>11</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>12</sup>University of California San Diego, San Diego, CA, USA, <sup>13</sup>Rush University Medical Center, Chicago, IL, USA

**Background:** Understanding factors that affect viral rebound timing during antiretroviral treatment interruption will accelerate efforts toward inducing sustained HIV remission. We evaluated whether immunologic parameters prior to treatment interruption are predictive of time to rebound in individuals interrupting ART in a highly monitored setting.

**Methods:** A5345 enrolled individuals who started ART in chronic or early infection and who were virally suppressed on ART for ≥2 yrs. Using flow cytometry, we evaluated frequencies of T cell maturation subsets, levels of T cell activation (HLA-DR+CD38+), exhaustion (PD-1, TIM3, TIGIT, LAG3, and CD160), and HIV-specific T cell polyfunctional responses (CD107a, TNFα, IL2, and IFNγ) to gag, pol, and env peptide pools. Principal component analysis (PCA) and Spearman correlation were used to evaluate time to rebound (≥1000 cps/mL), and parameters were compared between participants rebounding ≤3wks vs. ≥4wks (Wilcoxon).

**Results:** Of the 45 analyzed participants, 33 were treated in chronic infection. There were no consistent differences in the immune parameters between early and chronic-treated participants. Higher frequencies of T cells expressing activation and exhaustion markers via PCA were modestly associated with shorter time to viral rebound (r = -0.27, p = 0.07) whereas none of the HIV-specific immune parameters correlated with viral rebound. 29 and 16 participants had viral rebound ≤3wks and ≥4wks, respectively. The two groups did not differ in terms of levels of T cell activation and exhaustion, except for a trend for lower %LAG3+CD8+ T cells in the ≥4wk group (p = 0.06). The ≥4wk group also had greater %effector memory CD4+ T cells (p = 0.021) but lower %naive CD4+ T cells (p = 0.037). The ≥4wk group had lower absolute numbers of total CD8+ T cells expressing CD107a following HIV peptide pool stimulation (p = 0.05), and trends for lower % polyfunctional CD4+ T cell responses to pol (p = 0.07), env (p = 0.06) and total HIV peptide pool (p = 0.052).

**Conclusion:** Although no single immune marker was strongly predictive of time to rebound, higher levels of T cell activation and exhaustion while on ART are modestly associated with shorter time to rebound. In addition, those with early viral rebound had higher levels of on-ART HIV-specific T cells. Additional studies are needed to evaluate whether higher levels of proviral expression

and antigenic stimulation on ART may be responsible for immune stimulation, exhaustion and more rapid viral rebound after treatment interruption.

**312 MATHEMATICAL MODELING OF PREDICTORS OF POSTTREATMENT CONTROL IN HIV CURE TRIALS**

**Gesham Magombedze<sup>1</sup>, Devi SenGupta<sup>1</sup>, Jonathan Li<sup>2</sup>, Romas Geleziunas<sup>1</sup>, Steven G. Deeks<sup>3</sup>**

<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>2</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA

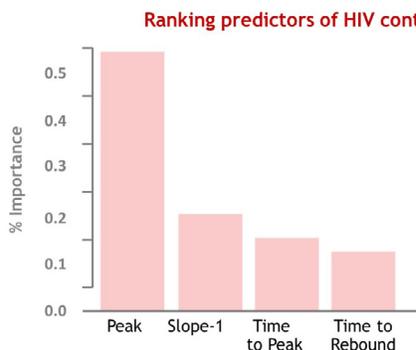
**Background:** Achieving an HIV cure or durable antiretroviral therapy (ART)-free HIV control is a significant unmet need. Due to the lack of validated predictors of virologic control, clinical trials rely on analytical treatment interruptions (ATI) to assess the efficacy of potential curative interventions. After ART is interrupted, a period of acute viremia occurs before the immune system responds, and a setpoint established. As this period of acute viremia poses risks to the participant and their sexual partners, algorithms that predict who will eventually control their virus might be helpful. Detailed studies of early viral dynamics in post-treatment controllers versus non-controllers may also provide insights into the development of an optimal therapeutic strategy.

**Methods:** We analyzed data from five AIDS Clinical Trials Group (ACTG) ATI studies (A371, A5024, A5068, A5187, A5197) and from the GS-US-382-3961 TLR7 study, in which prior controllers on ART interrupted therapy (N=134). Mathematical modeling and machine learning were used to identify early predictors of control at setpoint (defined by viral loads ≤400 c/mL at 2/3 of timepoints for ≥24 weeks). Our analysis replicated real time data collection in a clinical study, delineating outcomes for individuals who will become virologic controllers (N=20) from non-controllers.

**Results:** Our mathematical model identified the peak viral load, the rate of viral rebound (Slope-1), the time-to-peak and the time-to-rebound as the best predictors of virologic control following treatment interruption (Figure). These parameters identified individuals that became virologic controllers with accuracy, sensitivity and specificity scores of (i) ≥94% (Peak+Slope-1+Time-to-rebound), (ii) ≥89% (Peak+Time-to-rebound), and (iii) ≥78% (Peak). Statistical analysis showed that viral peak is the most important predictor (p<0.0001), then Time-to-rebound (p=0.0019) and Slope-1 (p=0.026).

**Conclusion:** Early identification of virologic controllers is important to improve the safety and efficiency of ATI trials. During the immediate post-ART period, peak viremia, the initial viral load slope and time-to-rebound predicted long-term post-treatment control. The quality of the host-response during the earliest stages of virus rebound may have long-term implications, suggesting that remission strategies will need to be optimized so that they are effective at the time the virus begins to spread systemically.

**Figure. Mathematical modeling identifies early predictors of virologic control.** Machine learning was applied to available ATI data to identify predictors of virologic control. This model identified the following as the top 4 predictors of control: peak HIV-1 viral load (Peak), rate of viral rebound (Slope-1), time-to-peak and the time-to-rebound. The respective sensitivity, specificity and accuracy scores (given in brackets) in descending order for different predictor combinations and individual predictors are as follows (i) Peak+Slope-1+Time-to-rebound (0.94,0.94,0.94), (ii) Peak +Time-to-rebound (0.89,0.95,0.92), (iii) Peak + Slope-1 (0.83,0.98,0.91), (iv) Peak (0.78,0.99,0.88), (v) Slope-1+Time-to-rebound (0.61,0.94,0.78), (vi) Slope-1 (0.39,0.97,0.68) and (vii) Time-to-rebound (0.22,0.97,0.60).



**313 THE SAO PAULO PATIENT: LOSING CELLULAR IMMUNITY AND REEMERGENCE OF DISTINCT HIV**

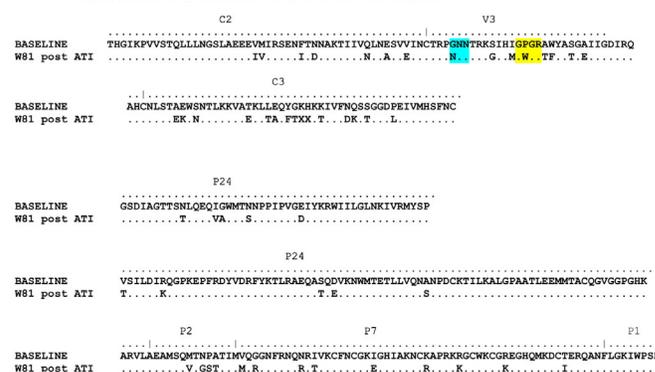
**Ricardo S. Diaz<sup>1</sup>, Leila B. Giron<sup>2</sup>, Juliana Galinskas<sup>3</sup>, James Hunter<sup>3</sup>, Muhammad S. Arif<sup>4</sup>, Sadia Samer<sup>4</sup>, Danilo Dias<sup>5</sup>, Luiz Mario R. Janini<sup>3</sup>, Iart Luca Shytaj<sup>5</sup>, Maria Cecilia A. Supcupira<sup>3</sup>, Juliana T. Maricato<sup>3</sup>, Mohammad M. Tarek<sup>6</sup>, Andrea Savarino<sup>7</sup>**  
<sup>1</sup>Federal University of Sao Paulo, Sao Paulo, Brazil, <sup>2</sup>Wistar Institute, Philadelphia, PA, USA, <sup>3</sup>Federal University of Sao Paulo, Sao Paulo, SP, Brazil, <sup>4</sup>Northwestern University, Chicago, IL, USA, <sup>5</sup>Heidelberg University, Heidelberg, Germany, <sup>6</sup>Armed Forces College of Medicine, Cairo, Egypt, <sup>7</sup>Aalborg University Hospital, Aalborg, Denmark

**Background:** A man seemingly cured of HIV was reported at the International AIDS Conference in 2020, sparking debate (Diaz et al, J Int AIDS Soc, 2020; 23(4):OAXLB0105). The patient had been subjected to a 5-drug antiretroviral regimen + nicotinamide, a drug aimed at disrupting HIV latency and boosting cell-mediated immunity (NCT02961829). He had been in antiretroviral analytical treatment interruption (ATI) for 68 weeks with viral loads (VL) below detection limits (BDL), progressively declining HIV-1, but not CMV, antibody titers. The present report investigates the long-term stability of post-ATI control.

**Methods:** Cell-mediated immune responses were evaluated in stored PBMC by ELISPOT using the patient-specific GAG peptides, generic HIV peptides (GAG-p6, p17, NEF, VIF, gp160), and CMV peptides at baseline, weeks (W) 12, 24, 36, and 48 (study period), W116 (regular ART), and W64 and W68 post-ATI. HIV-1 VL was determined monthly.

**Results:** MHC profiling showed no alleles associated with HIV-1 control and one allele associated with increased infection susceptibility (DRB1\*150:03). The patient displayed increasing cell-mediated responses against two highly conserved Gag epitopes predicted to optimally bind his Class I HLA during experimental therapy. After ATI, these responses progressively disappeared, in parallel to the linear decline of anti-HIV-1 Abs, whereas CMV ELISPOT remained high. At W74 post-ATI (September 11th 2020) patient was diagnosed with secondary syphilis. VL remained BDL until W76 post-ATI becoming detectable at W79 and W81 (both log<sub>10</sub>=3.8 cp/mL on Nov 9th and 23rd 2020). Emerging HIV strain has the Brazilian GWGR motif at the tip of the V3 loop of gp120, whereas baseline strain presented the GPGR motif and had an incomplete N-linked glycosylation site suggesting a strain subjected to evolution and immune escape. The gag sequence from the emerging strain had amino acid substitutions compared to the original strain, but not in motifs corresponding to epitopes towards which cell-mediated immunity was directed. C2-V3-C3 sequences from baseline and after viremia are 17.3% different, whereas gag sequences are 11.4% different (Figure).

**Conclusion:** Anti-Gag cell-mediated immunity was associated with unprecedented post-therapy VL control in the chronic phase of the disease. Analyses are ongoing to investigate if the viral rebound source is the reactivation of a mutated virus or a new infection.



**Figure:** Amino acid alignment of C2-V3-C3 regions of gp-120 (top) and gag (bottom) from baseline sample and sample collected upon viremia at 81 weeks post ATI. Dots indicates similarities, and X the presence of more than one amino acid at same position. The GPGR motif at the tip of the V3 loop is marked in yellow, and n-linked glycosylation site after the first cysteine is marked in blue. Sequences were obtained by bulk PCR from proviral DNA, and sequences from C2-V3-C3 regions obtained at weeks 20 and 44 during the intervention phase of the study are identical to the baseline sequence.

**314 A NOVEL EXTENDED-LENGTH HIV-1 PLASMA RNA SEQUENCING ASSAY**  
**Katie Fisher<sup>1</sup>**, Xiao Qian Wang<sup>1</sup>, Vincent Morcilla<sup>1</sup>, Ashley Lee<sup>1</sup>, Anthony Kelleher<sup>2</sup>, Sarah Palmer<sup>1</sup>

<sup>1</sup>The Westmead Institute for Medical Research, Westmead, Australia, <sup>2</sup>Kirby Institute, Sydney, Australia

**Background:** The genetic characterization of full-length plasma-derived HIV-1 RNA is critical for identifying genetically intact genomes, as well as identifying genomes that are similar to those sequenced from proviral DNA. This remains technically challenging due to the instability of the RNA genome. We have developed an efficient procedure to sequence individual near full-length HIV-1 RNA genomes.

**Methods:** The single-genome sequencing and full-length individual proviral sequencing assays were modified to allow for cDNA synthesis, PCR amplification at limiting dilution and sequencing of plasma-derived HIV-1 RNA genomes using primers spanning either GAG-3' (8.4kb) or INT-3' (5.1kb). Plasma samples from 2 untreated HIV-1-infected participants were diluted to copy numbers ranging from 10,000 to <50 copies to determine the lower limits and reproducibility of each region. To assess the extent of assay-related inter-template recombination, plasma samples containing 12000 HIV-1 RNA copies from each participant were mixed prior to RNA extraction and GAG-3' sequencing. The error rate of the assay was calculated by analysing 95 GAG-3' individual sequences (837520 total nucleotides) from PMA-activated J-Lat 10.3 culture supernatant.

**Results:** The lower limits of the GAG-3' and INT-3' assays were 350 copies and 40 copies, respectively. For the first participant (plasma collected approximately 1 month post-infection), 13.5% of GAG-3' sequences were found to be genetically identical (n=140). This increased to 32.3% of INT-3' sequences (n=93). For the second participant, whose plasma was collected during chronic infection, the GAG-3' sequences were unique (n=110), while 1.96% of INT-3' sequences were identical to another sequence (n=102). Using the GAG-3' assay, 70% of sequences from the first participant were genetically intact, while 50% from the second participant were intact. Most defects were caused by a frameshift mutation found in Env. No examples of inter-template recombination were observed in the 87 single GAG-3' genomes sequenced from the combined participant plasma. The error rate of the GAG-3' assay was determined to be 0.0074%.

**Conclusion:** We have developed an assay to sequence near full-length regions of the HIV-1 RNA genome present in the plasma of HIV-1-infected individuals. This assay will provide a new level of sensitivity for understanding the genetic composition of plasma-derived HIV-1 RNA and assessing the genetic composition of rebound virus during an analytical treatment interruption.

**315 QUANTIFICATION BIAS IN HIV-1 PROVIRUSES BY NEAR FULL-LENGTH GENOME SEQUENCING METHODS**

**Jennifer A. White<sup>1</sup>**, Joshua T. Kufera<sup>1</sup>, Niklas Bachmann<sup>1</sup>, Weiwei Dai<sup>1</sup>, Francesco Simonetti<sup>1</sup>, Annukka A. Antar<sup>1</sup>, Sunyoung Jang<sup>1</sup>, Katherine M. Jenike<sup>1</sup>, Subul Beg<sup>1</sup>, Jun Lai<sup>1</sup>, Gregory Laird<sup>2</sup>, Janet Siliciano<sup>1</sup>, Robert Siliciano<sup>3</sup>

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Accelevar Diagnostics, Baltimore, MD, USA, <sup>3</sup>Howard Hughes Medical Center, New York, NY, USA

**Background:** Antiretroviral therapy (ART) completely inhibits HIV-1 replication but is not curative due to the establishment of a latent reservoir in resting CD4+ T cells, which remains the major barrier to cure. Proviral sequencing provides critical insights on how to measure the reservoir and distinguish the excess of defective proviruses from the intact proviruses which give rise to viral rebound. Near full length genome sequencing (nFGS) methods carried out at limiting dilution provide an estimate of the quantity of intact proviruses and a qualitative picture of the common fatal defects including hypermutation and internal deletions. However, nFGS methods assume that there is a one to one correspondence between sequencing results and the actual frequency of proviruses. All nFGS methods rely on long distance PCR reactions, and interpretation of assay results are based on the assumption that all proviruses are amplified with equal efficiency regardless of length.

**Methods:** Here, we evaluate nFGS methods using the intact proviral DNA assay (IPDA) which quantitates intact and defective proviruses using short, highly efficient multiplex digital droplet PCRs. The IPDA can directly enumerate the number of product molecules generated by nFGS reactions. We measured the yield from nFGS reactions used in published reservoir assays on precisely quantitated templates with internal deletions of various lengths.

**Results:** We demonstrate that nFGS methods that employ long distance PCRs are extremely inefficient and underestimate full length (9kb) sequences by 70%. Deleted proviruses with shorter sequence length (3kb), representative of large internal deletions, were detected at a frequency of 96% and amplified with greater efficiency than full length proviruses.

**Conclusion:** These results demonstrate that reservoir assays that rely on nFGS do not give an accurate quantitative picture of the proviral landscape due to the inefficiency of long distance PCR. Accurate measurements of the latent reservoir of HIV-1 are critical in evaluating the efficacy of cure strategies. While nFGS methods provide detailed qualitative information, methods utilizing short highly efficient PCRs may provide a more accurate quantitative picture of the latent reservoir.

**316 IMPROVED DETECTION OF HIV Gag p24 PROTEIN FROM PATIENT-DERIVED SAMPLES**

**Guoxin Wu<sup>1</sup>**, Carol Cheney<sup>1</sup>, Qian Huang<sup>1</sup>, Daria Hazuda<sup>1</sup>, Bonnie Howell<sup>1</sup>, Paul Zuck<sup>1</sup>

<sup>1</sup>Merck & Co, Inc, Kenilworth, NJ, USA

**Background:** Sensitive assays aimed at quantifying translationally competent genomes are needed to understand the contribution of viral proteins to HIV-1 pathogenesis and determine the effectiveness of cure interventions. Sensitive assays have been previously used to detect HIV gag p24 in blood and tissues, but these detection approaches still leave gaps with sensitivity and selectivity due to sample matrix effects. Here we report on an immunoprecipitation (IP) step in our p24 Simoa assay to overcome these barriers, leading to improved detection and expanded applications.

**Methods:** Conditions were optimized for p24 immunocapture and for conditions which efficiently elute p24 from the beads and maintain compatibility with the downstream assay. We applied the assay to ex vivo simulated blood CD4+ T cells and to rectal biopsies from both viremic and aviremic donors. Additionally, we developed new methodology for the extraction of protein from rectal biopsies, eliminating single cell isolations to enhance and simplify the protocol to ensure all sources of p24 are measured. **Results:** IP of HIV gag p24 onto antibody-coated beads, followed by acidic elution and neutralization yielded nearly full recovery of all p24 in a sample. Validation of the approach was confirmed using recombinant p24 as well as patient-derived samples. Assay reproducibility was high and %CV was low as measured by inter-day experiments. Direct soaking of intact rectal pinch biopsies in a lysis solution showed release of all CD4 protein from the biopsy (a surrogate marker for target cells of interest). The new assay shows high recovery and reproducibly even at low concentrations of analyte.

**Conclusion:** Including an IP step, HIV gag p24 detection by Simoa has been enhanced. This combined assay can detect as low as 1 fg of p24 protein from a given sample volume. The removal of matrix proteins prior to the read step, reduces background and false positives, aiding in data interpretation for low-level protein expression. The IP method allows for directly lysis of all cells in a rectal biopsy without having background from matrix effects. These steps reduce assay labor and minimize cell and protein during processing. These enhancements open additional avenues for ex vivo study of LRAs or clearance approaches using patient-derived samples.

**317 ACCELERATED CEREBRAL BLOOD-FLOW REDUCTION AND BRAIN AGING IN PEOPLE LIVING WITH HIV**

**Kalen Petersen<sup>1</sup>**, Nicholas Metcalf<sup>1</sup>, Sarah Cooley<sup>1</sup>, Dimitre Tomov<sup>1</sup>, Florin Vaida<sup>2</sup>, Robert Paul<sup>3</sup>, Beau M. Ances<sup>1</sup>

<sup>1</sup>Washington University in St Louis, St Louis, MO, USA, <sup>2</sup>University of California San Diego, La Jolla, CA, USA, <sup>3</sup>University of Missouri St Louis, St Louis, MO, USA

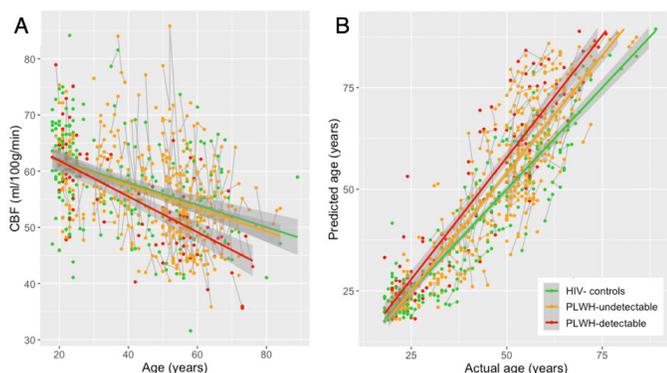
**Background:** People living with HIV (PLWH) are characterized by altered brain structure and function. As they attain normal lifespans, it remains unclear whether HIV accelerates aging in select subgroups. Additionally, the relationship between viral load (VL) and brain aging has not been fully investigated.

**Methods:** Three groups were evaluated: HIV uninfected (HIV-) controls (n=206), PLWH with undetectable VL (<=50 copies/mL; n=230), and PLWH with detectable VL (>50 copies/mL; n=93). A subset of individuals (n=201) completed longitudinal follow-up (mean=2.3 years post-baseline). T1-weighted structural imaging (TR/TE=2400/3.2ms) was used with a deep-learning algorithm to predict brain age based on a pre-trained model of healthy individuals. The gap between predicted and actual age ( $\Delta$ age) evaluated structural aging. Pseudo-continuous arterial spin labeling (TR/TE=3500/9.0ms,

labeling=1500ms, post-labeling delay=1200ms) was obtained to calculate gray matter cerebral blood flow (CBF). Cognition was assessed with a 15-test battery that covered five domains. Mixed-effects linear models tested the prediction that detectable HIV VL was associated with accelerated aging as measured by greater reduction in CBF or increased structural  $\Delta$ age. Age, sex, and race were included as covariates. Relationships between cognition and CBF or  $\Delta$ age were explored.

**Results:** Age-associated CBF decline was not different between PLWH and HIV-controls. However, CBF reduction was accelerated in PLWH who had detectable HIV VL vs. undetectable HIV VL ( $p=0.02$ , A). In general, PLWH had accelerated structural  $\Delta$ age increases vs. HIV- controls ( $p<0.001$ , B), while structural aging did not differ between PLWH who had detectable and undetectable HIV VL. These effects represented significant age\*group interactions. PLWH as a whole had reduced performance in executive function, psychomotor speed, and language, and those with detectable HIV VL had greater impairment in psychomotor speed and language ( $p<0.05$ ). No association was observed between CBF and cognition. Across all participants, psychomotor slowing was associated with increased  $\Delta$ age ( $p<0.001$ ).

**Conclusion:** Brain aging in PLWH included accelerated loss of gray matter perfusion and morphological alterations detected using machine learning. Cerebrovascular changes are sensitive to current HIV VL, while structural aging correlated with HIV serostatus but not HIV VL. Structural aging likely reflects cumulative gray and white matter degeneration, and is associated with cognitive function.



### 318 SEX DIFFERENCES IN WHITE-MATTER LOSS AND ASSOCIATED AXONAL INJURY IN PLWH

Erin Kelly<sup>1</sup>, Elizabeth Horne<sup>1</sup>, Kaniq Thomas<sup>1</sup>, Cynthia McMahan<sup>1</sup>, Ulisses Santamaria<sup>1</sup>, Hsing-Chuan Hsieh<sup>2</sup>, Xiuping Chu<sup>2</sup>, Joseph Snow<sup>1</sup>, Anuradha Ganesan<sup>2</sup>, Ryan C. Maves<sup>3</sup>, Gregory Utz<sup>3</sup>, Daniel Reich<sup>1</sup>, Avindra Nath<sup>1</sup>, Govind Nair<sup>1</sup>, Bryan R. Smith<sup>1</sup>

<sup>1</sup>National Institutes of Health, Bethesda, MD, USA, <sup>2</sup>Uniformed Services University of the Health Sciences, Bethesda, MD, USA, <sup>3</sup>Naval Medical Center San Diego, San Diego, CA, USA

**Background:** Studying sex differences in HIV-related co-morbidities has a global significance, as women now constitute the majority of adults aged 15 and over living with HIV worldwide. Specifically, higher levels of neurocognitive impairment have been reported in women living with HIV (WLWH) than men living with HIV (MLWH). This prompts the question of whether this difference is due to HIV-related brain changes in WLWH or better explained by other factors. Neuroimaging studies in people living with HIV (PLWH) have largely focused on comparing WLWH to women controls and MLWH to men controls or have studied one sex. By comparing brain volume proportion in virologically-controlled PLWH and controls of both sexes, we studied the effect of HIV and sex differences on brain health in the current era of widespread antiretroviral treatments.

**Methods:** Our prospective research cohort consists of virologically controlled PLWH and controls enrolled in a study of HIV and cognition. Volumetric measurements of participants' MRIs were computed using Freesurfer software. Volumes were converted to proportions by dividing each by estimated total intracranial volume (eTIV), thus adjusting for skull size. To examine trends in volume loss over time, total brain, white matter, and gray matter proportions were plotted against age in each group to calculate slopes. Neurofilament light chain (NFL) in CSF was measured using the Quanterix Simoa platform.

**Results:** 286 scans from PLWH and 105 from age-matched controls were analyzed by Freesurfer. Brain volume proportions were overall higher in women compared to men ( $p < 0.001$  Tukey's multiple comparisons test) irrespective of HIV status. When looking at white and gray matter individually, results in Table 1 show significant differences between groups specifically in white matter slopes with evidence for the greatest loss of white matter over time in MLWH ( $p = 0.0151$ ). A subset of participants (MLWH= 46, WLWH = 22) had CSF NFL measured concurrent with MRI. In this group, we found higher median NFL levels in MLWH compared to WLWH ( $p=0.02$ ), suggesting axonal neurodegeneration following the same pattern as found in MRI sex differences.

**Conclusion:** In this well-characterized cohort of treated PLWH there are clear differences in brain volume proportions by sex with results suggesting MLWH may have more white matter loss over time that is associated with axonal damage.

Table 1: Comparisons of MRI Proportions and Slopes

|                                | MLWHIV          | Men-controls    | WLWHIV          | Women-controls  | P value |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|---------|
| N (Freesurfer)                 | 195             | 59              | 91              | 46              |         |
| Age                            | 53.31<br>(8.27) | 54.07<br>(9.47) | 54.87<br>(7.26) | 52.95<br>(7.42) | 0.4199  |
| Brain proportion (SD)          | 0.70 (0.05)     | 0.70 (0.05)     | 0.75 (0.07)     | 0.74 (0.06)     | <0.001  |
| Brain proportion slope*        | -0.002621       | -0.002253       | -0.001942       | -0.002041       | 0.8473  |
| White matter proportion (SD)   | 0.30 (0.02)     | 0.30 (0.02)     | 0.32 (0.03)     | 0.32 (0.02)     | <0.001  |
| White matter proportion slope* | -0.0009875      | -0.0006417      | 0.0002685       | -0.0004896      | 0.0151  |
| Gray matter proportion (SD)    | 0.38 (0.03)     | 0.38 (0.04)     | 0.41 (0.04)     | 0.40 (0.04)     | <0.001  |
| Gray matter proportion slope*  | -0.001551       | -0.001523       | -0.002213       | -0.001677       | 0.7083  |
| CSF NFL median pg/ml           | 807 (n=46)      | 619 (n=13)      | 575 (n=22)      | 407 (n=10)      | <0.001  |

\*slope = proportion over age in years

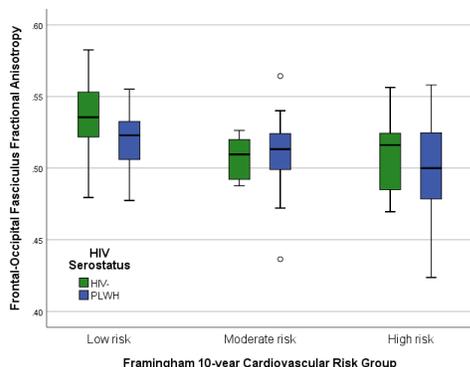
### 319 THE EFFECTS OF CARDIOVASCULAR HEALTH ON WHITE MATTER IN HIV+ AND HIV- PERSONS

Sarah Cooley<sup>1</sup>, Jeremy Strain<sup>1</sup>, Collin B. Kilgore<sup>1</sup>, Beau M. Ances<sup>1</sup>  
<sup>1</sup>Washington University in St Louis, St Louis, MO, USA

**Background:** Cardiovascular health has been linked to changes in brain structure and function in the HIV-negative (HIV-) population. However, results are still mixed as to how HIV and indicators of cardiovascular health may affect brain integrity, as measured by neuroimaging, in people living with HIV (PLWH). **Methods:** 48 HIV- and 166 PLWH virologically well-controlled on stable combination antiretroviral therapy for >12 months, aged 30-80 years, completed cognitive testing and a magnetic resonance imaging scan, from which diffusion tensor imaging (DTI) values were computed to assess white matter microstructural integrity. Differences in Framingham Heart Study Cardiovascular Disease (10-year risk) scores (FRS) were evaluated between HIV- and PLWH. Multivariate general linear models assessed main effects and interactions between HIV serostatus and FRS categories (low risk=0-9, moderate risk=10-19, high risk= $\geq 20$ ) on cognitive performance, and fractional anisotropy (FA) from 12 white matter tracts in the brain. Spearman's correlations examined relationships between cognitive performance and tract FA.

**Results:** FRS was higher in PLWH (mean=17.8, SD=10.0) compared to HIV- (mean = 11.1, SD=9.4) ( $p<0.001$ ). Individuals in the moderate and high risk FRS groups performed significantly worse on tests of psychomotor speed compared to those in the low risk group ( $p$ -values <.01) regardless of HIV serostatus. There were no significant interactions between HIV and FRS ( $p$ -values>.05). There were no significant main effects of HIV serostatus on FA within the selected white matter tracts. However, regardless of HIV serostatus individuals in the moderate and high FRS groups demonstrated significantly lower FA of the frontal aslant tract ( $p$ -values <.01), frontal-occipital tract ( $p$ -values <.01; Fig 1), and the inferior longitudinal fasciculus ( $p$ -values <.01) compared to individuals in the low FRS group. There were no significant HIV and FRS interactions ( $p$ -values>.05) on FA measures. In general, lower FA was associated with poorer psychomotor speed performance ( $p$ -values<.001) regardless of HIV status.

**Conclusion:** PLWH demonstrate a significantly higher 10-year risk for cardiovascular disease compared to HIV- individuals, and that risk was associated with reduced cognitive performance and microstructural integrity of major white matter tracts in the brain. Cardiovascular health represents a potentially modifiable risk factor for reduced brain integrity in both HIV- and PLWH and should be treated in all individuals.



**320 VASCULAR INJURY MARKERS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN HIV PATIENTS ON ART**

**Debjani Guha<sup>1</sup>, Vikas Misra<sup>1</sup>, Sukrutha Chettimada<sup>1</sup>, David Lorenz<sup>2</sup>, Dana Gabuzda<sup>1</sup>**  
<sup>1</sup>Dana–Farber Cancer Institute, Boston, MA, USA

**Background:** HIV-associated neurocognitive disorders (HAND) remain prevalent despite viral suppression on current antiretroviral therapy (ART). Cerebrovascular disease contributes to HAND, but biomarkers that distinguish vascular cognitive impairment from other types of HAND remain unclear. In this cross-sectional study, we investigated relationships between plasma and CSF vascular, inflammation, and CNS injury markers, HAND, and cerebrovascular disease in HIV+ subjects on ART.

**Methods:** Vascular injury (ICAM-1, VCAM-1, CRP), inflammation (IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-8, IL-15, IP-10, MCP-1, VEGF-A), and CNS injury (total Tau, GFAP, YKL-40) markers were measured in plasma and CSF samples collected from subjects enrolled in NNTC and CHARTER between 2006–2015 using the Meso Scale Discovery (MSD) platform in 207 subjects (143 HIV+ virally suppressed on ART, age 30–75 years, 85% male, 71% white, 73 with HAND diagnoses of asymptomatic neurocognitive impairment (ANI) or mild neurocognitive disorder (MND) and 70 without HAND, and 64 HIV- controls matched for age, gender, race). CSF and plasma albumin levels were measured and CSF-plasma albumin ratio (Qalb) was calculated.

**Results:** The median age of HIV+ participants was 52 years (IQR 47 – 58) and median CD4 count, CD4 nadir, plasma viral load, and duration of HIV infection were 504 cells/ul, 76 cells/ul, 50 HIV copies/ml, and 16.5 years, respectively. HIV+ subjects had higher ICAM-1, CRP, IL-8, IL-15, IP-10, and VEGF in plasma and higher CRP, IP-10, VEGF, and GFAP in CSF compared with HIV- controls ( $p < 0.05$ ). Plasma ICAM-1, VCAM-1, CRP, and YKL-40 and CNS injury markers (CSF total Tau, GFAP, YKL-40) were increased in HAND vs. no HAND or HIV- control groups and correlated negatively with neurocognitive T scores ( $p < 0.05$ ). In contrast, most inflammation markers had weak or no significant associations with HAND and T scores. Cerebrovascular disease was more prevalent among HAND compared with no HAND subjects, and was associated with increased levels of VCAM1 and YKL-40 in plasma and increased total Tau and YKL-40 in CSF ( $p < 0.05$ ). We did not detect significant associations between Qalb and plasma or CSF biomarkers. **Conclusion:** Peripheral markers of vascular injury are more closely related to HAND and CNS injury in HIV patients on current ART than markers of inflammation, and may help to distinguish relative contributions of vascular cognitive impairment to HAND in this population.

**321 SEX-SPECIFIC ASSOCIATIONS BETWEEN CSF MARKERS AND COGNITIVE FUNCTION IN PWH IN UGANDA**

**Alyssa Vecchio<sup>1</sup>, Dionna Williams<sup>2</sup>, Yanxun Xu<sup>3</sup>, Danyang Yu<sup>3</sup>, Deanna Saylor<sup>2</sup>, Sarah Lofgren<sup>4</sup>, Riley O'Toole<sup>3</sup>, David Boulware<sup>4</sup>, Thomas Quinn<sup>2</sup>, Maria Wawer<sup>5</sup>, Ned Sacktor<sup>2</sup>, Leah Rubin<sup>2</sup>**

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>4</sup>University of Minnesota, Minneapolis, MN, USA, <sup>5</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** People with HIV (PWH) taking antiretroviral therapy (ART) have persistent cognitive impairment. The prevalence of cognitive impairment is higher in women with HIV compared to men with HIV, possibly due to sex differences in immune function. Here we report sex differences in cerebrospinal

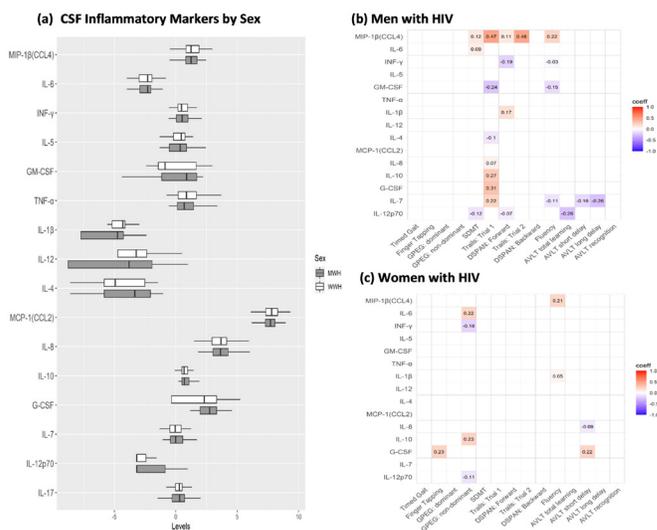
fluid (CSF) immune markers in relation to cognitive performance in the context of ART mediated viral suppression.

**Methods:** A subset of 83 PWH on ART (52% women; mean age=37.6 years) from the Rakai community cohort study Cohort and Rakai Health Sciences Program supported clinics in rural Uganda completed a neuropsychological (NP) assessment and a lumbar puncture. CSF was used to measure 16 cytokines/chemokines via multiplex profiling with Luminex Platform (Human 17-Plex Panel, Bio-Rad, Hercules, CA). Individual NP test z-scores were generated based on local normative data. A series of least absolute shrinkage and selection operator (lasso) regressions examined associations between CSF inflammatory markers and NP outcomes after adjusting for alcohol use and pre-ART log viral load.

**Results:** In the absence of sex-differences in overall levels of CSF inflammatory markers ( $P > 0.05$ , Figure 1a) the number and patterns of cognitive correlates of neuroinflammation differed by sex (Figure 1 b, c) Among men, eleven of the sixteen markers were associated with NP outcomes with MIP-1 $\beta$ , IL-7, and IL-12p70 correlating with most outcomes. Conversely, women had fewer associations between inflammatory markers and NP outcomes, where each marker only correlated with one or two outcomes. Sociodemographic and clinical factors were similar by sex.

**Conclusion:** Women with HIV have previously been shown to be more vulnerable to immune dysfunction and impaired cognition compared to men, including exhibiting higher CSF HIV viral loads. Here we find that men have a larger number of associations between CSF biomarkers and cognitive outcomes than women in the context of similar levels of CSF biomarkers of inflammation in men and women. Some of these patterns indicate a positive relationship between immune regulation and cognition, particularly in men. Our findings provide initial evidence that neuroinflammation may contribute to sex differences in cognition in PWH. Further investigation in larger cohorts and longitudinal studies may lead to delineation of sex-specific mechanisms of cognitive dysfunction in HIV and, possibly impact sex-specific screenings and management to limit the neurological complications of HIV in the ART era.

**Figure 1. Log CSF inflammatory markers did not differ by sex (A); however, the number and pattern of CSF inflammatory markers relating to cognitive outcomes using a series of LASSO regressions differed in men (B) and women with HIV (C).** Each LASSO regression was fitted 100 times and CSF marker significant on 90% of the regressions were considered significant in their association with that NP outcome. Note. This statistical approach has been shown to yield satisfactory false discovery control. Coeff=unstandardized beta coefficient. GPEG=Grooved Pegboard; SDMT=Symbol Digit Modalities Test; DSPAN=Digit Span; AVLT=Auditory Verbal Learning Test.



**322 CIRCULATING INTERMEDIATE MONOCYTES: A COGNITIVE BIOMARKER IN HIV-INFECTED WOMEN**

**Rebecca Veenhuis<sup>1</sup>, Dionna Williams<sup>1</sup>, Erin Shirk<sup>1</sup>, Celina Abreu<sup>1</sup>, Edna Ferreira<sup>1</sup>, Jennifer Coughlin<sup>1</sup>, Todd Brown<sup>1</sup>, Pauline Maki<sup>2</sup>, Kathryn Anastos<sup>3</sup>, Joan Berman<sup>3</sup>, Janice Clements<sup>1</sup>, Leah Rubin<sup>1</sup>**

<sup>1</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>University of Illinois at Chicago, Chicago, IL, USA, <sup>3</sup>Albert Einstein College of Medicine, Bronx, NY, USA

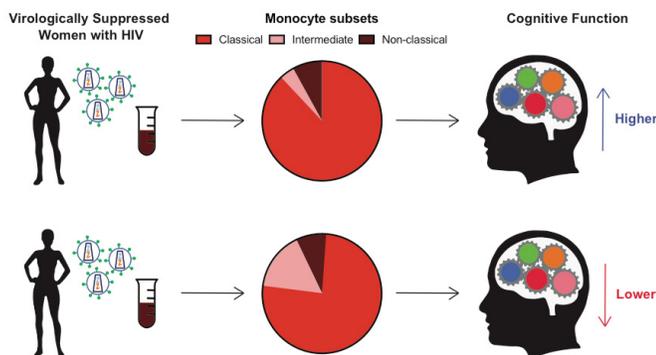
**Background:** Identifying a quantitative biomarker of neuropsychiatric dysfunction in people with HIV (PWH) remains a significant challenge in the neuroHIV field. The strongest evidence implicates the role of monocytes

in central nervous system (CNS) dysfunction in HIV. Studies have assessed monocyte subsets combined with other markers (CCR2, sCD163, sCD14, HIV DNA). However, no study has examined the proportion of monocyte subsets in blood as a correlate and/or predictor of neuropsychiatric function in PWH in the era of modern antiretrovirals.

**Methods:** In two independent cohorts of virologically suppressed women with HIV (WWH; n=19 and n=18), whole blood samples were obtained either in conjunction with neuropsychiatric assessments (neuropsychological [NP] battery, depression and stress-related symptom questionnaires) or one year prior to the clinical assessments. Immune cell proportions were assessed in whole blood or freshly isolated PBMCs by flow cytometry. To examine associations between total monocytes, monocyte subsets, T-cell populations, and neuropsychiatric outcomes, we conducted Spearman's Rho correlations (rs). Adjusted analyses were not required as none of our measured variables (age, CD4 count) met the definition of being a confounder.

**Results:** A higher proportion of intermediate (CD14++CD16+) monocytes was associated with lower global NP function when assessing monocytes concurrently (rs=-0.60, P=0.006) and approximately one year before (predictive) NP testing (rs=-0.54, P=0.02). The same pattern was seen for mental flexibility (concurrent: rs=-0.53, P=0.01; predictive: rs=-0.68, P=0.003) and processing speed (concurrent: rs=-0.58, P=0.009; predictive: rs=-0.65, P=0.003). Conversely, there were no associations with monocyte subsets and mental health symptoms. However, lower CD4 T cell proportions were associated with higher perceived stress (rs=-0.58, P=0.03). A higher proportion of classical monocytes was also associated with better cognition (rs=0.48-0.67, P's<0.05).

**Conclusion:** It is widely accepted that lentiviral infection of the CNS targets cells of monocyte-macrophage-microglial lineage and is associated with an increase in intermediate monocytes in the blood and monocyte migration into brain. However, the proportion of intermediate monocytes in blood of virally suppressed WWH has never been directly associated with cognition. Our findings provide initial evidence for a new, easily measured blood-based cognitive biomarker in WWH.



### 323 BASELINE MONOCYTE HIV RNA PREDICTS BLUNTED COGNITIVE TRAJECTORIES IN ACUTE INFECTION

**Ivo Sahbandar**<sup>1</sup>, Carlo Sacdalan<sup>2</sup>, Eun Young Park<sup>3</sup>, Phillip Chan<sup>2</sup>, Andrew Belden<sup>4</sup>, Nittaya Phanuphak<sup>5</sup>, Jocelyn Liu<sup>1</sup>, Kamonkan Tangnaree<sup>2</sup>, Eugene Kroon<sup>2</sup>, Victor Valcour<sup>6</sup>, Jintanat Ananworanich<sup>6</sup>, Sandhya Vasan<sup>7</sup>, Serena S. Spudich<sup>8</sup>, Robert Paul<sup>4</sup>, Lishomwa Ndhlovu<sup>1</sup>, for the RV254/SEARCH 010 Study Team  
<sup>1</sup>Weill Cornell Medicine, New York, NY, USA, <sup>2</sup>SEARCH, Institute of HIV Research and Innovation, Bangkok, Thailand, <sup>3</sup>University of Hawaii at Manoa, Honolulu, HI, USA, <sup>4</sup>Missouri Institute of Mental Health, University of Missouri, St. Louis, St. Louis, USA, <sup>5</sup>University of California San Francisco, San Francisco, CA, USA, <sup>6</sup>University of Amsterdam, Amsterdam, Netherlands, <sup>7</sup>US Military HIV Research Program, Bethesda, MD, USA, <sup>8</sup>Yale University, New Haven, CT, USA

**Background:** Even when instituted during acute HIV infection (AHI), antiretroviral therapy (ART) does not completely prevent brain injury. Peripheral biomarkers of monocyte/macrophage activation are strong indicators of brain abnormalities in HIV. Whether early establishment of HIV in monocytes contributes to viral persistence and brain injury remains unknown. Here we determined the detectability of HIV RNA in monocytes and evaluated the levels of monocyte HIV RNA in acute HIV infection and its utility to predict long-term cognitive deficits following ART.

**Methods:** We isolated monocytes to ultra-high purity by flow cell sorting from cryopreserved peripheral blood mononuclear cells from 30 Thais who initiated ART during AHI (Fiebig stages I-IV). Total monocyte HIV RNA was assessed by real-time PCR at baseline and 96 weeks post-ART. Neuropsychological (NP) tests comprising Color Trails (CT; 1 and 2), Trail Making A (TM-A), and Grooved Pegboard (GP) were performed at baseline and weeks 24, 96, and 144 post-ART in 28 participants. Liquid array-based immunoassay was used to measure plasma myeloid activation and proinflammatory markers (soluble) sCD14, sCD163, neopterin, IL-1, IL-6, IL-8, IL-12 and IL-23) at baseline in 19 participants. Comparison between groups were performed using Wilcoxon Rank Sum test.

**Results:** Participants were mostly male (96.7%), with a median age of 26 years. Monocyte HIV RNA was detected in 17 of 30 (57%) participants at baseline and in 3 of 30 (10%) post-ART. NPZ-4 and the subdomains of CT1, CT2, and TM-A improved post-ART compared to baseline (all p values <0.05). Individuals with detectable monocyte HIV RNA at baseline exhibited significantly less improvement in CT1 performance compared to individuals with undetectable monocyte virus (p=0.014). The trajectory of performance on TM-A was lower in participants with detectable vs. undetectable monocyte HIV RNA from baseline through 144 weeks post-ART (p=0.05). Baseline plasma sCD14, sCD163, neopterin, IL-6, IL-12 and IL-23 trended higher in individuals with detectable vs. undetectable baseline monocyte HIV RNA (p<0.56).

**Conclusion:** Despite early initiation and two years of continuous ART, detectable monocyte HIV RNA at baseline was associated with delayed improvement in cognitive status suggesting that early establishment of HIV in monocytes represents a viable predictor of cognitive outcomes. Additional interventions may be required to preserve brain health in people with HIV even when identified during acute infection.

### 324 GLYCA IS ASSOCIATED WITH NEUROPSYCHOLOGICAL IMPAIRMENT IN PREDOMINANTLY HIV+ MEN

**Albert M. Anderson**<sup>1</sup>, Fiona Bhondoekhan<sup>2</sup>, Dusica Curanovic<sup>3</sup>, Marge Connelly<sup>3</sup>, James Otvos<sup>3</sup>, Wendy Post<sup>2</sup>, Erin D. Michos<sup>4</sup>, Cecile D. Lahiri<sup>1</sup>, Steven Wolinsky<sup>5</sup>, Andrew Levine<sup>6</sup>, Eric C. Seaberg<sup>4</sup>, Leah Rubin<sup>4</sup>, David Vance<sup>7</sup>, James Becker<sup>8</sup>, for the MACS WHHS Combined Cohort Study

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>3</sup>LabCorp, Morrisville, NC, USA, <sup>4</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>5</sup>Northwestern University, Chicago, IL, USA, <sup>6</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>7</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>8</sup>University of Pittsburgh, Pittsburgh, PA, USA

**Background:** Neuropsychological impairment (NPI) remains prevalent among people with HIV (PWH) in the combination antiretroviral therapy (ART) era. The mechanisms for NPI during ART remain unclear, but accumulating evidence suggests that chronic inflammation may have a role. GlycA, a novel blood biomarker representing the nuclear magnetic resonance signal from glycosylated acute phase reactants, is associated with coronary artery disease in PWH and may have additional promise as a marker of NPI.

**Methods:** We performed a cross-sectional analysis of HIV+ and HIV-negative men within the Multicenter AIDS Cohort Study (MACS), in which participants underwent regular comprehensive neuropsychological (NP) testing involving six domains. NP test scores are normalized based on age, sex, race, education, and previous test administration. NPI was present if two or more domains were at least one standard deviation below the mean, as per 2007 HIV Frascati criteria. In addition to GlycA, plasma concentrations of CRP, IL-6, CCL2, sCD163, and sCD14 were measured. We examined associations between NPI and blood biomarkers using univariable and multivariable logistic regression incorporating medical covariables.

**Results:** A total of 843 men were studied. 63% were HIV+, of whom 92% were on ART. In univariable analysis, increased levels of GlycA, CRP, and sCD14 (all p<0.01) as well as increased sCD163 (p<0.05) were associated with the presence of NPI. Hepatitis C (HCV) positivity was also associated with NPI. Among HIV+ participants, current detectable HIV RNA as well as cumulative HIV RNA over time (both p<0.01) were associated with NPI. In multivariable analysis that adjusted for enrollment wave, BMI, estimated GFR (eGFR), and HCV status (Table), GlycA remained significantly associated with impairment. This was particularly true in HIV+ participants. Of models that incorporated the inflammatory biomarkers individually, CRP was the only biomarker significantly associated with NPI in addition to GlycA. When examining the association by tertile of CRP, GlycA was significantly associated with NPI only in the highest tertile of CRP.

**Conclusion:** Higher GlycA levels were independently associated with NPI in the MACS. GlycA therefore may be a durable window into NPI pathogenesis during HIV. Participants with higher CRP levels contributed significantly to this finding, suggesting that GlycA may be most valuable in the setting of increased overall inflammation, which is common during HIV.

Table: Models for the association between GlycA and Neuropsychological impairment

| Model type  | GlycA (umol/l)               |  |                          |
|---|------------------------------|--|--------------------------|
|   | Overall N=843<br>OR [95% CI] | HIV-uninfected<br>N=315<br>OR [95% CI] | PWH N=528<br>OR [95% CI] |
| Univariable   | 1.43*[1.15, 1.79]            | 1.51*[1.01, 2.25]                      | 1.38*[1.06, 1.80]        |
| Adjusted <sup>†</sup>                                 | 1.40*[1.12, 1.76]            | 1.37[0.90, 2.09]                       | 1.33*[1.01, 1.75]        |
| CRP adjusted <sup>†</sup>                             | 1.29*[1.02, 1.64]            | 1.25[0.80, 1.95]                       | 1.25[0.94, 1.66]         |
| CRP stratified – 1 <sup>st</sup> tertile <sup>†</sup> | 1.13[0.69, 1.85]             | 1.89[0.82, 4.37]                       | 0.80[0.41, 1.54]         |
| CRP stratified – 2 <sup>nd</sup> tertile <sup>†</sup> | 1.23[0.81, 1.89]             | 1.07[0.48, 2.38]                       | 1.21[0.72, 2.03]         |
| CRP stratified – 3 <sup>rd</sup> tertile <sup>†</sup> | 1.79*[1.22, 2.63]            | 1.50[0.68, 3.29]                       | 1.84*[1.17, 2.89]        |

Exponentiated coefficients; 95% confidence intervals in brackets;

<sup>†</sup>p < 0.05, \*\*p < 0.01;

<sup>†</sup>Models additionally adjusted for: MACS enrollment wave, BMI, eGFR, and HCV status.

### 325 PREDICTED PATHOGENICITY OF mtDNA VARIANTS AND MOTOR IMPAIRMENT IN PERSONS WITH HIV

**Karen E. Volpe**<sup>1</sup>, David Samuels<sup>2</sup>, Jannetta Steyn<sup>3</sup>, Joanna L. Elson<sup>3</sup>, Ronald J. Ellis<sup>4</sup>, Robert K. Heaton<sup>4</sup>, Asha R. Kallianpur<sup>5</sup>, Scott Letendre<sup>4</sup>, Todd Hulgan<sup>1</sup>  
<sup>1</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>2</sup>Vanderbilt University, Nashville, TN, USA, <sup>3</sup>Newcastle University, Newcastle, UK, <sup>4</sup>University of California San Diego, San Diego, CA, USA, <sup>5</sup>Cleveland Clinic, Cleveland, OH, USA

**Background:** Mitochondrial DNA (mtDNA) variation is associated with neurocognitive (NC) impairment (NCI) in persons with HIV. Prior studies have focused on mtDNA haplogroups. Recent models consider the cumulative impact of mtDNA variants predicted to be deleterious. MutPred software uses sequence conservation and protein structure to predict the impact of mtDNA variants on protein function. We examined MutPred pathogenicity scores in the CHARTER study, hypothesizing that persons with deleterious variants would be more likely to have NCI.

**Methods:** The CHARTER study included NC testing in persons with HIV from 2005–2008. MutPred pathogenicity scores were assigned to CHARTER participants with full mtDNA sequence; any single score >0.5 is considered potentially deleterious. Cross-sectional outcomes at cohort entry were NCI, defined by the global deficit score and seven NC domain deficit scores (DDS), and by global and domain-specific mean T-scores (TS). Univariate comparisons used Wilcoxon rank sum and Fisher's exact tests. Multivariable models were adjusted for age, sex, nadir CD4+ T-cell count, antiretroviral therapy, NC comorbidity status (incidental vs. contributing), and ancestry (European vs. non-European). Secondary analyses were ancestry-stratified.

**Results:** Data were available for 744 persons (357 African ancestry; 317 European). In univariate analysis of the overall cohort, the presence of any potentially deleterious variant was associated with motor impairment, with impaired persons less likely to have a deleterious variant (41 vs. 56%, p=0.001). In multivariable analysis, the presence of any deleterious variant remained associated with both motor impairment (p=0.03) and motor TS (p=0.05). In ancestry-stratified multivariable analyses, motor-domain impaired individuals of European and African ancestry were less likely to have a deleterious variant, although these results were not statistically significant (p=0.06–0.08). There was no significant association between motor TS and the presence of any deleterious variant in ancestry-stratified models.

**Conclusion:** Predicted pathogenicity of mtDNA variants was associated with motor performance in persons living with HIV, with impaired individuals significantly less likely to have any deleterious variant. These findings suggest that potentially deleterious variants may unexpectedly confer protection against impaired motor performance, perhaps through neuro-muscular pathways. Further studies are needed to explore the basis of these effects.

### 326 BUCCAL MITOCHONDRIAL DNA IS ASSOCIATED WITH AMYLOID-β 1-42 IN CEREBROSPINAL FLUID

**Dipesh Solanki**<sup>1</sup>, Adam J. Fields<sup>1</sup>, Ronald J. Ellis<sup>1</sup>, Igor Grant<sup>1</sup>, Robert K. Heaton<sup>1</sup>, Scott Letendre<sup>1</sup>, Sanjay R. Mehta<sup>1</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA

**Background:** Damage to mitochondrial (mt) genomes over time contributes to physiologic aging. Human immunodeficiency virus (HIV) infection is associated with premature aging, but measuring its impact is difficult due to a lack of reliable biomarkers. The mtDNA common deletion mutation (mtCDM) is a 4977-bp deletion associated with aging and neurodegenerative diseases.

We examined how mtDNA copies per cell (cpc) and mtCDM cpc correlate with markers of neurodegeneration and inflammation.

**Methods:** Data from 149 adults were combined from two projects involving people with and without HIV (PWH and PWOH): 1) 78 PWH and 2) 46 PWH, 25 PWOH. We measured mtDNA and mtCDM cpc from buccal swabs by digital droplet PCR. Using univariable and stepwise multivariable regression, we compared them to disease and demographic characteristics and soluble biomarkers in cerebrospinal fluid (CSF) and blood measured by immunoassay.

**Results:** Median age of participants was 52 years, 81% men, and 53% white. Among PWH, 96% took antiretroviral therapy (ART, median 13.6 months); plasma HIV RNA was ≤200 cp/mL in 91%; and median CD4+ T-cell count was 595/μL. Median mtDNA level was 301 cpc (range 35.9 – 1432.2) and median mtCDM was 1.26 x 10<sup>3</sup> cpc (0 – 14.7 x 10<sup>3</sup>) and both were higher in PWH (mtDNA: d=1.45, mtCDM: d=0.89, both p<0.0001). In the best model adjusting for HIV status and demographics, higher mtDNA cpc were associated with higher amyloid-β 1-42 (p=0.0005) and higher sTNFR-II (p=0.042) in CSF (model R<sup>2</sup> = 0.37). The association with amyloid-β 1-42 held in the subgroup of PWH, even after adjusting for duration of HIV (p=0.08) and ART (p=0.13), and nadir (p=0.53) and current (p=0.22) CD4+ count (model p<0.0001). Higher mtCDM cpc were associated with higher plasma sTNFR-II levels (p=0.004) but no CSF biomarkers.

**Conclusion:** Buccal mtDNA is positively associated with amyloid-β 1-42 in CSF and both mt biomarkers were positively associated with sTNFR-II. Increased mtDNA cpc may indicate greater amyloid-β and sTNFR efflux from the brain into CSF. Further studies are needed to understand the concomitantly increased mtCDM, but this may reflect an increase in mt activity and oxidative stress due to HIV and ART effects in the brain. Our findings also support the use of affordable, easily accessible buccal specimens as a screening tool for inflammation and amyloid-β in CSF. Additional confirmatory and mechanistic studies on mt genome alteration by HIV and ART may identify interventions to prevent or treat neurodegenerative complications.

### 327 CSF MARKERS OF AD-RELATED PATHOLOGY AND MEMORY DEFICITS IN OLDER PEOPLE WITH HIV

**Judith D. Lobo**<sup>1</sup>, Erin E. Sundermann<sup>1</sup>, Mark W. Bondi<sup>1</sup>, Ben Gouaux<sup>1</sup>, Cristian L. Achim<sup>1</sup>, Scott Letendre<sup>1</sup>, David J. Moore<sup>1</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA

**Background:** Older people with HIV (PWH) are at-risk for Alzheimer's disease (AD) and its precursor, amnesic mild cognitive impairment (aMCI). Identifying aMCI among PWH is challenging because memory impairment is also common in HIV-associated neurocognitive disorders (HAND). The neuropathological hallmarks of aMCI/AD are amyloid-42 (Aβ42) plaque and phosphorylated tau (p-tau) accumulation. We assessed whether the AD pathology markers of lower Aβ42 levels and higher p-tau and p-tau/Aβ42 ratio levels in the cerebrospinal fluid (CSF) could help identify early stages of aMCI among older PWH with high rates of HAND. We assessed the relationship of these AD CSF biomarkers to learning and memory performance versus other neurocognitive domains that are more commonly-impaired in HAND than in aMCI (motor and speed of information processing).

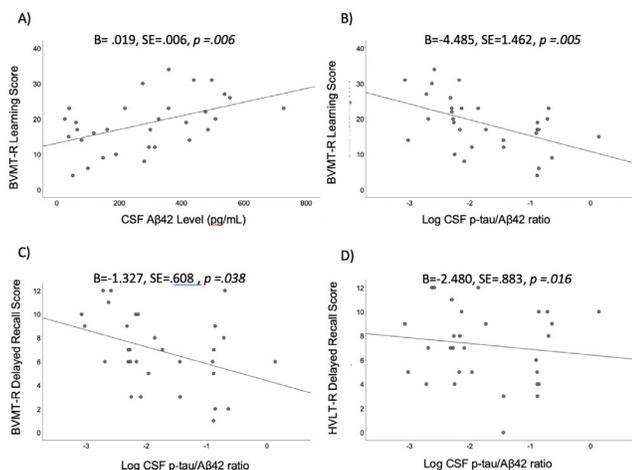
**Methods:** Participants included 31 PWH aged 50–68 years (84% male, 58% White) from the National NeuroAIDS Tissue Consortium (NNTC). CSF Aβ42 and p-tau were measured by commercial immunoassay. The analyzed neurocognitive domains included: learning and memory (Hopkins Verbal Learning Test-Revised and Brief Visuospatial Memory Test-Revised), speed of information processing (WAIS-III Digit Span) and motor (Grooved Pegboard Test). Linear regressions examined the relationship between neurocognitive scores and levels of CSF p-tau, Aβ42, and p-tau/Aβ42 ratio while adjusting for demographics, apolipoprotein-E ε4 genotype, HIV disease characteristics (nadir CD4, antiretroviral treatment status) and clinical comorbidities (e.g., substance use disorders).

**Results:** Forty-five percent of participants were diagnosed with HAND. Lower CSF Aβ42 levels related to poorer BVMT-R Learning (p=.006; Figure 1). Higher CSF p-tau/Aβ42 ratio related to poorer BVMT-R Learning, and BVMT-R and HVLT-R Delayed Recall (ps<.05). CSF p-tau levels did not relate to neurocognitive test scores. Motor and speed of information processing were not significantly related to AD CSF biomarkers.

**Conclusion:** The specificity of the relationship between CSF AD biomarkers and learning/memory performance suggests that these biomarkers, particularly p-Tau/Aβ42 ratio, have utility in identifying aMCI/AD-related cognitive deficits

amid a background of HAND. Additional research is needed to fully identify, among PWH, who is at greatest risk for aMCI/AD and whether there is increased risk for aMCI/AD among PWH as compared to those without HIV.

**Figure 1.** Scatterplots showing significant CSF AD biomarker associations among the regression models particularly in the domains of learning and memory: A) CSF A $\beta$ 42 concentration and BVMT-R Learning Score, B) CSF p-tau/A $\beta$ 42 ratio and BVMT-R Learning Score, C) CSF p-tau/A $\beta$ 42 ratio and BVMT-R Delayed Recall Score D) CSF p-tau/A $\beta$ 42 ratio and HVLT Delayed Recall Score.



### 328 HIGHER COMORBIDITY BURDEN PREDICTS WORSENING NEUROCOGNITION IN PEOPLE WITH HIV

Ronald J. Ellis<sup>1</sup>, Emily W. Paolillo<sup>1</sup>, Rowan Saloner<sup>2</sup>, Scott Letendre<sup>2</sup>, David J. Moore<sup>1</sup>, Robert K. Heaton<sup>2</sup>

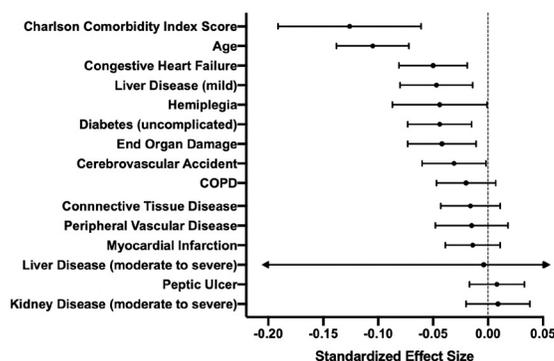
<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>University of California San Diego, San Diego, CA, USA

**Background:** Comorbidities linked to aging such as diabetes mellitus, visceral adiposity and renal dysfunction accumulate at a faster rate in people with HIV (PWH) than in the general population. We evaluated whether the Charlson Index, a global comorbidity scale comprising 17 variables that has been validated in previous studies, predicted neurocognitive trajectories in PWH.

**Methods:** Neurocognition was measured by averaging scaled scores from all assessments in a comprehensive neuropsychological battery. Multilevel modeling was used to examine between- and within-person predictors of global neurocognition. At the between-person level, average Charlson Index (averaged within each person across all their visits) was examined as a predictor of neurocognitive change over time, covarying for the effect of HIV disease characteristics (proportion of visits virally suppressed, average CD4). At the within-person level, Charlson Index was used to predict fluctuations in global neurocognition at the same and next visit, covarying for visit-specific effects of viral load detectability and current CD4 count.

**Results:** Participants were 1195 PWH (mean age at baseline = 43.0; SD 9.7) followed for an average of over 7.1 years (SD = 5.0; range = 0.5 to 20.5 years). Between persons, higher average Charlson index scores were associated with faster rates of global neurocognitive decline (standardized  $\beta$  = -0.50 [0.015],  $p$  = 0.001). This global effect was driven by significant decline in the domains of executive functioning ( $p$  = 0.001) and working memory ( $p$  = 0.007). The Figure shows the contributions of individual components of the Charlson. HIV disease characteristics did not predict trajectories of neurocognitive change ( $ps > 0.05$ ). At the within-person level of the model, lower current CD4+ lymphocytes ( $\beta$  = 0.043 [0.009];  $p < 0.001$ ), detectable plasma HIV RNA ( $\beta$  = 0.018 [0.006];  $p = 0.001$ ), and higher Charlson Index score ( $\beta$  = -0.046 [0.015];  $p = 0.003$ ) related to worse concurrent global neurocognitive performance at the same visit. Time-lag analyses demonstrated that increasing comorbidities occurred concomitant with, not before, neurocognitive decline.

**Conclusion:** The impact of comorbidities on trajectories of neurocognitive decline was greater than that of HIV disease factors. Although correlative, the temporal relationship between accumulating comorbidities and neurocognitive decline suggests that interventions to prevent or ameliorate a variety of comorbidities may improve neurocognitive prognosis for PWH.



### 329 NEUROCOGNITIVE DYSFUNCTION, INFLAMMATION, AND ADIPOSITY IN TREATED HIV PATIENTS

Vanessa E. El Kamari<sup>1</sup>, Corrielyn O. Hileman<sup>2</sup>, Danielle Labbato<sup>1</sup>, Julia Kosco<sup>1</sup>, Grace A. McComsey<sup>1</sup>

<sup>1</sup>University Hospitals Cleveland Medical Center, Cleveland, OH, USA, <sup>2</sup>MetroHealth Medical Center, Cleveland, OH, USA

**Background:** The advances in ART have decreased the incidence of the severe form of HIV-associated neurocognitive disorders; however, milder impairment have emerged. The pathogenesis of this milder form of neurocognitive decline remains poorly understood.

**Methods:** This is a cross-sectional study involving 65 HIV+ and 33 matched HIV - controls recruited at University Hospitals Cleveland Medical Center. For the first time in HIV, we used cognitive, an FDA-approved computer-based test. This test was approved for identifying potential decline in cognitive function and is calibrated to an individual's unique cognitive ability. Six cognitive testing domains (visuospatial, memory, executive function, naming/language, delayed recall, and abstraction) and two performance parameters (speed processing and reaction time) were measured. Markers of inflammation, immune activation, insulin resistance, and body fat composition (by DEXA scan) were collected. Classical t-test, chi-square tests, and spearman correlations were used to compare and explore relationships between variables.

**Results:** Overall, 53% were male, 47% were African American, with a mean age of 43 years. Among HIV + individuals, all were on ART by design and 80% had an undetectable HIV-1 RNA level ( $\leq 20$  copies/ml). Compared to controls, HIV+ participants had a lower overall cognitive score (76% vs 83%,  $p = 0.01$ ), and performed poorer across different cognitive domains (visuospatial, memory, executive function, naming/language, delayed recall, and abstraction, (all  $p < 0.05$ )). In performance testing domains, HIV+ participants had significantly longer adaptive motor control reaction time (mean 588 +/- 178ms vs 509 +/- 138 ms,  $p < 0.05$ ) and processing speed time (1679 +/- 145ms vs 1633 +/- 89 ms,  $p < 0.05$ ). However, there were no significant differences in the visual salience reaction time between the two groups ( $p = 0.3$ ). In the HIV+ group, lower cognitive testing domain scores were associated with higher inflammatory markers (IL6, TNFR-I, TNFR-II, hsCRP), and with higher body fat compositions (total percent fat and visceral adipose tissue). On the other hand, only significant associations were observed between cognitive domain scores and TNFR-I in HIV-controls.

**Conclusion:** For the first time in HIV, our results highlight the potential implications of inflammation, immune activation, and body fat composition measures in neurocognitive impairment among HIV-infected adults, suggesting a potential new therapeutic target for HIV-associated neurocognitive decline in this population.

**330 DEMENTIA INCIDENCE AMONG ART-TREATED PEOPLE WITH HIV IN A PRIMARY CARE SETTING**

**Jennifer O. Lam<sup>1</sup>**, Paola Gilsanz<sup>1</sup>, Catherine Lee<sup>1</sup>, Craig E. Hou<sup>2</sup>, Wendy Leyden<sup>1</sup>, Derek D. Satre<sup>3</sup>, Jason Flamm<sup>4</sup>, William J. Towner<sup>5</sup>, Michael A. Horberg<sup>6</sup>, Michael J. Silverberg<sup>1</sup>

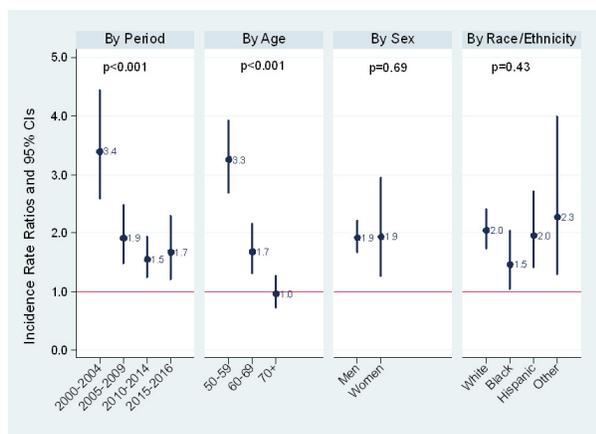
<sup>1</sup>Kaiser Permanente Northern California, Oakland, CA, USA, <sup>2</sup>Kaiser Permanente Northern California, South San Francisco Medical Center, South San Francisco, CA, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA, <sup>4</sup>Kaiser Permanente Northern California, Sacramento Medical Center, Sacramento, CA, USA, <sup>5</sup>Kaiser Permanente Southern California, Pasadena, CA, USA, <sup>6</sup>Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA

**Background:** People aging with HIV may be at increased risk for dementia. However, few studies have compared the incidence of dementia between people with HIV (PWH) on antiretroviral therapy (ART) and people without HIV (PWoH) in primary care.

**Methods:** We conducted a cohort study of individuals aged ≥50 years who were members of Kaiser Permanente health plans in Northern California, Southern California, and Mid-Atlantic States (Maryland, Virginia, Washington D.C.) between 2000 and 2016. PWH and PWoH were frequency-matched 1:10 by age, sex, race/ethnicity, medical facility, and calendar year at baseline. We excluded PWH without an ART prescription fill in the year before baseline. Incident all-cause dementia diagnoses were identified in electronic health records using International Classification of Diseases codes confirmed via chart review in ~300 randomly selected patients. Dementia incidence was evaluated by HIV status using Poisson regression models adjusted for period (2000-2004, 2005-2009, 2010-2014, 2015-2016), age (50-59, 60-69, ≥70 years), sex, race/ethnicity (White, Black, Hispanic, Other), and healthcare utilization (outpatient visit frequency in the year before baseline). An overall model adjusted for all covariates. Subsequent adjusted models were stratified by period, age, sex, and race/ethnicity.

**Results:** The study included 11,302 PWH and 154,620 uninfected individuals (mean baseline age=53 years, 11% female; 82% of PWH with HIV RNA<200 copies/ml). During follow-up (mean=8 years), 264 PWH and 2,006 PWoH developed dementia. Crude incidence of dementia was 4.4 (95% CI=3.9-4.9) and 2.1 (95% CI=2.0-2.2) per 1,000 person-years in PWH and PWoH, respectively (incidence rate ratio [IRR]=2.0, 95% CI=1.8-2.3). After covariate adjustment, incidence remained higher in PWH (IRR=1.9, 95% CI=1.7-2.2). In models stratified by age, IRR was highest in younger age groups (age 50-59, IRR=3.3, 95% CI=2.7-3.9; age 60-69, IRR=1.7, 95% CI=1.3-2.1) but normalized in those age ≥70 (IRR=1.0, 95% CI=0.7-1.3). In models stratified by period, IRR decreased over time but remained elevated among PWH in the most recent (2015-2016) period (IRR=1.7, 95% CI=1.2-2.3). There were no significant differences in incidence across sex and race/ethnicity strata.

**Conclusion:** Despite ART use, dementia incidence is higher among PWH compared with PWoH and is diagnosed at younger ages. Further research is needed to determine factors contributing to age-specific patterns and continued elevated dementia incidence among ART-treated PWH.



Reference group = People without HIV; CI = confidence interval. Models are adjusted for period, age, sex, race/ethnicity, and healthcare utilization. P values in the plots indicate the significance of differences in dementia incidence comparing people with and without HIV in analyses stratified by time period, age group, sex and race/ethnicity. These p values were obtained models with interaction terms for HIV\*period, HIV\*age, HIV\*sex and HIV\*race/ethnicity.

**331 PWH AND ALZHEIMER'S DISEASE RISK: CLARIFYING THE HAND PHENOTYPE OVER TIME**

**David J. Moore<sup>1</sup>**, Anya Umlauf<sup>1</sup>, Florin Vaida<sup>1</sup>, Scott Letendre<sup>1</sup>, Mark W. Bondi<sup>1</sup>, Erin E. Sundermann<sup>1</sup>

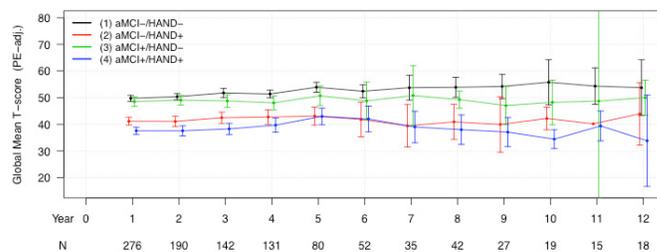
<sup>1</sup>University of California San Diego, La Jolla, CA, USA

**Background:** Older people with HIV (PWH) are at risk for Alzheimer's Disease (AD) and its precursor, amnesic Mild Cognitive Impairment (aMCI). Whereas aMCI/AD diagnoses require memory impairment, the neuropsychological domains impaired for a diagnosis of HIV-associated Neurocognitive Disorders (HAND) are varied and can include memory, which presents a challenge in identifying aMCI/AD among older PWH. We aimed to classify PWH by both aMCI and HAND status, and then compare cognitive functioning trajectories by aMCI/HAND diagnosis. We hypothesized that PWH classified as aMCI, with or without HAND, would evidence more rapid decline over time.

**Methods:** The sample included 265 mid-to-late life (45+ years old) PWH, (89% male and 65% Caucasian) from the HIV Neurobehavioral Research Program (HNRP) and the National NeuroAIDS Tissue Consortium (NNTC). All participants completed a comprehensive 7-domain neuropsychological battery with data from at least two visits (up to 10 visits). We applied neuropsychological criteria to identify aMCI in PWH (Bondi et al., 2014). HAND diagnoses were assigned using the Frascati criteria. After baseline aMCI/HAND assignment, global cognitive trajectories were compared between groups using linear mixed-effects models with subject-specific random intercept and slopes and fixed terms for grouping and time. AIC was used to select the best-fitting trajectory curve.

**Results:** The diagnostic categorizations were: aMCI+/HAND+ (n=95), aMCI+/HAND- (n=25), aMCI-/HAND+ (n=65), aMCI-/HAND- (n=81). As expected, both HAND groups had lower baseline global cognitive T-scores as compared to the non-HAND groups (all ps<0.05; Fig 1). No significant differences were observed between the groups in terms of plasma HIV viral load, duration of HIV disease, or ART treatment status (on/off). The aMCI+/HAND+ group was, on average, 11 global T-score points lower as compared to the aMCI-/HAND- group. Using the linear (best-fitting) model to examine trajectories over time, we found no significant decline from baseline in any of the aMCI/HAND groups (p=0.28; Fig. 1).

**Conclusion:** Regardless of aMCI and/or HAND grouping, there was stability in global cognitive function over time among PWH. Contrary to expectations, PWH with aMCI diagnoses were not more likely to decline. Given the heterogeneous HAND phenotype, it is imperative that we develop methods to identify aMCI/AD in HAND to accurately treat the underlying neurobiology.



**Figure 1.** Global Mean T-Score Trajectories Over Time by aMCI/HAND Group among PWH 45+ years old; Diagnostic Category Determined at Baseline

**332 EPIGENETIC AGING ASSOCIATED WITH COGNITIVE IMPAIRMENT IN OLDER BLACK ADULTS WITH HIV**

**Stephanie Shiau<sup>1</sup>**, Yanhan Shen<sup>2</sup>, Anyelina Cantos<sup>2</sup>, Christian Vivar Ramon<sup>2</sup>, Jayesh Shah<sup>2</sup>, Grace Jang<sup>2</sup>, Jennifer J. Manly<sup>2</sup>, Adam M. Brickman<sup>2</sup>, Andrea A. Baccarelli<sup>2</sup>, Stephen M. Arpadi<sup>2</sup>, Michael T. Yin<sup>2</sup>

<sup>1</sup>Rutgers School of Public Health, Piscataway, NJ, USA, <sup>2</sup>Columbia University Medical Center, New York, NY, USA

**Background:** Several studies detected epigenetic age acceleration using a DNA methylation (DNAm)-based biomarker of aging in people with HIV (PWH), but data in African Americans (AA), women, and older PWH are lacking. We assessed if HIV infection is associated with epigenetic age acceleration in AA older adults, and evaluated if epigenetic age acceleration is associated with cognitive function.

**Methods:** We measured DNAm in whole blood using Illumina EPIC Arrays in 107 (69 HIV+ and 38 HIV- controls) AA men and women ages 60-75 living in New York City. We estimated three age acceleration measures, where

positive values indicate that the blood sample is older than expected based on chronological age: epigenetic age acceleration (EAA), extrinsic epigenetic age acceleration (EEAA), and intrinsic epigenetic age acceleration (IEAA). The NIH Toolbox Cognition Battery was used to assess cognitive function across five domains: executive function, attention, working memory, processing speed, and language. We compared age acceleration measures between groups using t-tests and assessed correlations between age acceleration measures and standardized cognitive function scores, by HIV group.

**Results:** The HIV+ and HIV- groups did not differ by sex (49 vs 42% female), chronological age (65 vs 66 years), ethnicity (93% not Hispanic or Latino), frailty by Fried criteria (36 vs. 32%), or mean BMI (28.5 vs 30.9 kg/m<sup>2</sup>). 83% of the HIV+ had a viral load <50 copies/mL and 94% had a recent CD4 ≥200 cells/μL. Blood cell composition differed between groups, largely driven by higher proportions of CD8 (0.35 vs 0.18, p<0.01) and lower proportions of CD4 T-Cells (0.23 vs. 0.38, p<0.01) in the HIV+ group. Chronological age correlated with DNAm age (r=0.36, p<0.01). HIV+ had a higher mean EAA (2.4±8.5 vs -4.3±5.6, p<0.01) and EEAA (1.4±10.4 vs -2.5±5.6, p<0.01) compared to HIV-. IEAA was not significantly different between groups (0.2±6.1 vs -0.4±5.0, NS). There were negative linear relationships between EAA and IEAA and attention (r=-0.24, p=0.058; r=0.26, p=0.03, respectively) and working memory (r=-0.26, p=0.03; r=-0.30, p=0.01) for the HIV group, but not the controls.

**Conclusion:** Epigenetic age acceleration in blood was observed in AA older PWH using two measures, including EEAA which reflects immunosenescence. There was no evidence of age acceleration independent of cell type composition (IEAA) associated with HIV, but this measure was associated with decreased cognitive function in the HIV group.

### 333 RANDOMIZED CONTROLLED TRIAL OF MARAVIROC FOR HIV-ASSOCIATED NEUROCOGNITIVE IMPAIRMENT

**Cecilia M. Shikuma**<sup>1</sup>, Lindsay Kohorn<sup>1</sup>, Valerie Wojna<sup>2</sup>, Bruce Shiramizu<sup>1</sup>, Rosa J. Rodriguez-Benitez<sup>2</sup>, Emilee H. Turner<sup>1</sup>, Kalpana Kallianpur<sup>1</sup>, Scott Souza<sup>1</sup>, Andrew Belden<sup>3</sup>, Jacob Bolzenius<sup>3</sup>, Nancy Hanks<sup>1</sup>, Miriam Matos<sup>2</sup>, Lishomwa Ndhlovu<sup>1</sup>, Robert Paul<sup>3</sup>

<sup>1</sup>University of Hawaii at Manoa, Honolulu, HI, USA, <sup>2</sup>University of Puerto Rico, San Juan, Puerto Rico, <sup>3</sup>University of Missouri St Louis, St Louis, MO, USA

**Background:** It has been suggested that CCR5 antagonist maraviroc (MVC) improves HIV-associated neurocognitive impairment (NCI).

**Methods:** A double-blind, placebo-controlled, 48-week, randomized study of MVC vs placebo in people living with HIV (PLWH) on stable ART>1 year with plasma HIV RNA <50 copies/ml and at least mild neurocognitive impairment (NCI) defined as an overall or domain-specific (e.g., executive function, psychomotor speed, attention, and learning and memory) neuropsychological (NP) score < -0.5. Study participants, recruited from Hawaii (HI; n=26) and Puerto Rico (PR; n=22) (ClinicalTrials.gov NCT02159027), were randomized 2:1 to intensification of antiretroviral therapy (ART) with MVC vs with placebo. The primary endpoint was change in global and domain-specific NP Z scores (NPZ) modeled from study entry to week 48. Group comparisons were performed using a two-sample T-test.

**Results:** A total of 48 participants were entered into the study with 31 individuals randomized to MVC intensification and 17 to placebo. Study follow-up in PR was substantially impacted by Hurricane Maria leaving 39 evaluable subjects (HI 24; PR 15) who completed the final week 48 visit. At baseline, individuals randomized to the two arms were similar in age (median for both groups of 57), gender distribution (MVC vs placebo: 45% vs 53% male), current CD4 (667 vs 693 cells/mm<sup>3</sup>), self-reported nadir CD4 (150 vs 130 cells/mm<sup>3</sup>), years HIV positive (22 vs 17 years) and years on ART (17 yrs for both groups), but differed significantly by global NPZ score [MVC: -1.04 (0.62) vs placebo: -0.50 (0.44), p=0.002]. Comparison of change from baseline to week 48 in the two arms (table) revealed significant improvement in the MVC arm in the Learning and Memory NPZ domain, but not in the other domains or global NPZ. The group difference in the Learning and Memory domain score did not survive adjustment for multiple comparisons, although the effect size was 0.89.

**Conclusion:** This preliminary randomized controlled study found no definitive evidence in favor of MVC intensification for HIV-associated NCI. Blood biomarker analyses are pending.

Table: 48-Week Change in NPZ Global and Sub-Domain Composites

| NPZ Composite 48-Week Change | Maraviroc (N = 25) | Placebo (N = 14) | P-Value |
|------------------------------|--------------------|------------------|---------|
| Global                       | 0.02 (0.47)        | 0.09 (0.24)      | 0.601   |
| Attention                    | 0.004 (0.53)       | 0.19 (0.57)      | 0.300   |
| Motor                        | -0.29 (1.11)       | 0.03 (0.39)      | 0.189   |
| Psychomotor                  | 0.09 (0.79)        | 0.01 (0.66)      | 0.763   |
| Executive                    | 0.01 (0.80)        | 0.13 (0.78)      | 0.640   |
| Language                     | 0.06 (0.82)        | 0.33 (0.70)      | 0.324   |
| Learning and Memory          | 0.41 (0.53)        | -0.10 (0.61)     | 0.009   |
| Visuospatial                 | -0.03 (0.52)       | 0.32 (0.64)      | 0.071   |

48-week change calculated as baseline NP subtracted from week 48 NP. Two-sample T-tests used to compare differences between groups. Mean (standard deviation) shown. Unadjusted p-values reported.

### 334 IMPACT OF SWITCH FROM EFV/F/TDF TO B/F/TAF ON PSYCHIATRIC SYMPTOMS AND NEUROCOGNITION

**Alessandra Vergori**<sup>1</sup>, Carmela Pinnetti<sup>1</sup>, Patrizia Lorenzini<sup>1</sup>, Giulia Del Duca<sup>1</sup>, Ilaria Mastroianni<sup>1</sup>, Marta Camici<sup>1</sup>, Sandrine Ottou<sup>1</sup>, Federico De Zottis<sup>1</sup>, Elisabetta Grilli<sup>1</sup>, Maria Maddalena Plazzi<sup>1</sup>, Stefania Cicalini<sup>1</sup>, Rita Bellagamba<sup>1</sup>, Andrea Antinori<sup>1</sup>

<sup>1</sup>Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy

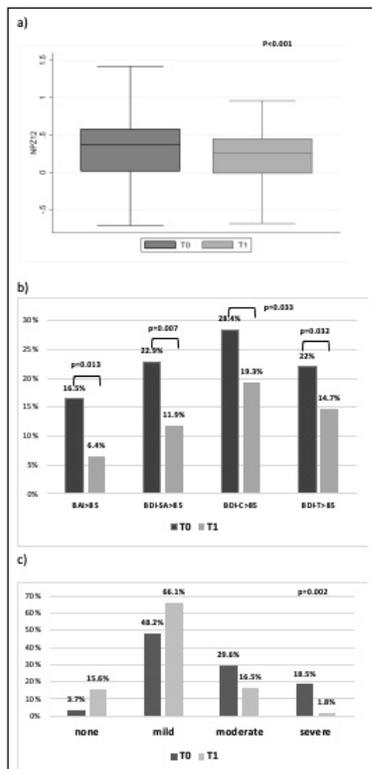
**Background:** EFV has been associated with neuropsychiatric side effects and sleep disorders, while association with neurocognitive impairment (NCI) remains controversial. Our aim was to investigate whether a treatment switch from EFV/F/TDF to B/F/TAF may improve psychiatric symptoms, sleep function and if it has an impact on neurocognition.

**Methods:** EBONY is a pilot, single arm, open label, prospective study of HIV suppressed patients (pts) on the efficacy and safety of switching from EFV/F/TDF to B/F/TAF. All pts underwent neuropsychological assessment (NPA) at the switch (T0) and after 48 weeks (T1). NPA was carried out through a standardized battery of 12 tests (5 domains). Participants were classified as having NCI if they scored >1 standard deviation (SD) below the normal mean in at least 2 tests, or >2 SD below in 1 test. Individual z-scores were determined, and NPZ-12 was calculated as the average of the 12 test z-scores; changes of NPZ-12 were analyzed as outcome. HAND was classified by Frascati's criteria. Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and Pittsburgh Sleep Quality Index (PSQI) were administered. Paired Wilcoxon and McNemar tests were used for statistical comparisons. Multivariable linear regression was used to find factors associated with changes in tests.

**Results:** 109 participants: mostly Caucasian male with a median age of 53 yrs (IQR 46-58), 30% MSM, median education 13yrs, 8% with at least 1 comorbidity and median CD4 count of 604 cells/mm<sup>3</sup> (500-810). The median time of EFV/F/TDF therapy was 8.4 yrs (7.1-10.1). NPA revealed a NCI in 36/109(33%) pts at T0 and 37/109(34%) at T1 (p=0.866). Specifically: 67.9% pts did not change at T1, 16.5% worsened and 15.6% improved. At T1 we observed a slight worsening in the NC function (mean±SD NPZ12 change: -0.21;+0.36; p<0.001; Figure 1a) and in mental flexibility (-0.16;+0.63; p=0.003), working memory (-0.47;+0.75); p<0.001) and memory (-0.28; +0.85; p<0.001) domains. We observed an ANI in 3.7% at T0 and 7.3% at T1. No pts with MND or HAD were found. Self-reported BAI and BDI-II questionnaires revealed an improvement at T1 (Figure 1b). Also sleep disorders significantly improved (Figure 1c). No factor associated with test score changes was found.

**Conclusion:** Our results suggest that switch from EFV/F/TDF to B/F/TAF significantly improves psychiatric symptoms and sleep disorders. Neurocognitive performance remained substantially stable, even though a decline on NPZ-12 and in specific domains was observed.

Figure 1. a) Comparison of NP212 score at the time of switch (T1) and after 48 weeks (T2), b) of patients proportion for Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI-SA, somatic-affective, BDI-C, cognitive, BDI-T, total) and c) for Pittsburgh Sleep Quality Index (PSQ)



**335 THE USE OF LESS NEUROTOXIC ANTIRETROVIRALS: SECONDARY ENDPOINTS OF THE MARAND-X STUDY**

**Andrea Calcagno**<sup>1</sup>, Veronica Pirriatore<sup>1</sup>, Silvia Orlando<sup>2</sup>, Giacomo Stroffolini<sup>1</sup>, Ambra Barco<sup>1</sup>, Giulia Guastamacchia<sup>2</sup>, Giuseppe Noce<sup>3</sup>, Cristiana Atzori<sup>2</sup>, Mattia Trunfio<sup>1</sup>, Lorenzo Mighetto<sup>2</sup>, Letizia Marinaro<sup>1</sup>, Giovanni Di Perri<sup>1</sup>, Stefano Bonora<sup>1</sup>  
<sup>1</sup>University of Turin, Turin, Italy, <sup>2</sup>ASL Città di Torino, Turin, Italy, <sup>3</sup>IRCCS SDN, Naples, Italy

**Background:** Despite a high prevalence (30-50%) HIV-associated neurocognitive disorders pathogenesis is incompletely understood. antiretrovirals' neurotoxicity has been suggested as a potential mechanism. Aim of the study was to measure the change in resting EEG waves, CSF biomarkers and Fibroscan measurements in PLWH with HAND randomized to a less neurotoxic regimen (darunavir/cobicistat, maraviroc, emtricitabine "MARAND") or continuing their treatment.

**Methods:** Adult PLWH with HAND were enrolled if presenting no major resistance-associated mutations, not on efavirenz>/darunavir, with RS-tropic HIV, without major confounding conditions, >6 months after HCV-SVR and with plasma and CSF HIV RNA <50 copies/mL. After 1:1 randomization, tests were repeated at 24 weeks: resting EEG, CSF biomarkers (HIV-RNA, tau, p-tau, Beta-amyloid1-42, S100Beta and neopterin). The freeware LORETA (low resolution brain electromagnetic tomography) was used for the estimation of EEG rhythms. Data are expressed as median (interquartile range). Non-parametric tests (Mann-Whitney and Wilcoxon's) were used.

**Results:** Results: In June 2020 the study was prematurely terminated for slow accrual when 38 participants were enrolled (19 per arm). Male (76.3%) and European ancestry (92.1%) were prevalent. Median age was 55 years (51-60). Plasma and CSF HIV RNA were <20 copies/mL in 33 (86.8%) and 32 (84.2%) participants; median CD4+ count was 626 cell/uL (469-772). Baseline characteristics were similar between the study arms. LORETA delta and alpha waves were similar at baseline and W24 (n=29). A significant decrease in parietal delta waves was observed in the MARAND arm (-0.69, p=0.022) but not in other waves or cortical sources. CSF HIV-RNA (n=14) was detectable in 43-44% participants at baseline and W24 with no significant difference. A significant decrease in CSF p-tau (-14.6 pg/mL, p=0.018) and an increase in CSF neopterin (+1.87 ng/mL, p=0.045) were observed in the MARAND arm.

Fibroscan (n=25) stiffness and coefficient attenuation parameter (CAP) were similar at baseline and W24: we observed a significant reduction in stiffness at W24 in the MARAND arm (-0.8 KPa, p=0.038).

**Conclusion:** Conclusions: Despite a small sample size we observed improvement in EEG cortical sources and in hepatic stiffness in patients randomized to the experimental arm. CSF biomarkers changes (lower phosphorylated-tau and higher neopterin) need to be replicated in large cohorts.

**336 PEMBROLIZUMAB FOR PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IN PLWH**

**Carmela Pinnetti**<sup>1</sup>, Eleonora Cimini<sup>1</sup>, Valentina Mazzotta<sup>1</sup>, Alessandra Vergori<sup>1</sup>, Federica Forbici<sup>1</sup>, Annalisa Mondì<sup>1</sup>, Germana Grassi<sup>1</sup>, Alessandra Amendola<sup>1</sup>, Susanna Grisetti<sup>1</sup>, Francesco Baldini<sup>1</sup>, Veronica Bordonì<sup>1</sup>, Paolo Campioni<sup>1</sup>, Maria Rosaria Capobianchi<sup>1</sup>, Chiara Agrati<sup>1</sup>, Andrea Antinori<sup>1</sup>

<sup>1</sup>Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy

**Background:** PML is a severe demyelinating disease occurring in advanced HIV infection, caused by the reactivation of poliovirus JC (JCV). In absence of specific anti JCV therapy, immunity restoration induced by effective combined antiretroviral treatment (cART) is a possible treatment strategy. The rationale on Pembrolizumab (PEM) use for treatment of PML is the inhibition of programmed cell death protein 1 (PD-1) potentially improving anti JCV-specific response with consequent JCV clearance.

**Methods:** We used PEM (2 mg/kg/iv every 4 wks) with cART for treatment of PML. The drug was given on a compassionate-use basis and all patients (pts) provided written informed consent. At each administration were performed clinical evaluation, MRI and laboratory testing, including immunophenotyping (CD3, CD4, CD8, PD-1 markers) in blood and CSF by flow cytometry. JCV specific T-cells response was analysed by Elispot assay after stimulation with JCV peptides. HIV-1 RNA was quantified with the Aptima® HIV-1 Quant Dx assay (Hologic) with a LoQ of 30 cps/ml, JCV DNA by an in house RealTime PCR method on LightCycler (Roche), targeting VP1, with LoD of 150 cps/ml.

**Results:** At present, 5 HIV+ pts enrolled: 4 male, median age 43 yrs (29-52), median CD4 and CD8 count 150 (15-158) and 973 (354-1250) cell/mm<sup>3</sup>, respectively; median JCV-DNA and HIV-RNA in CSF/plasma pairs 9,540/1,503 cps/mL and 2,230/619 cp/mL. All pts received at least two doses, with a maximum of seven doses (in pt1). After treatment, we observed a JCV-DNA decline in all pts (median change -0.42, -1.64, -0.09 log). 3/5 pts showed a stability of the clinical picture and neuroimaging (pt1, pt3 and pt4), and two others died (pt2 and pt5). PD-1 expression was high in circulating CD4 and CD8 at baseline, gradually decreased over time and remained stable at low level in all patients. Expression of PD-1 in CSF was higher than in the peripheral blood, even though lower after PEM. All pts experienced an improvement of JCV-specific T cell response after PEM that paralleled PD-1 decrease and JCV-DNA decay both in CSF and in plasma; all pts still alive showed undetectable JCV-DNA values in both compartments.

**Conclusion:** According to these preliminary data, JCV-DNA quantitative reduction, PD-1 down regulation and enhanced JCV-specific T-cell response after pembrolizumab was observed, even though clinical and radiological response remained poor. More data are needed in order to identify predictors of response to therapy.

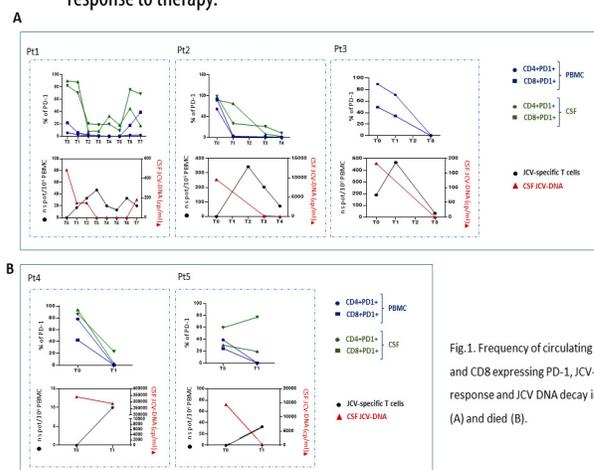


Fig. 1. Frequency of circulating and CSF CD4 and CD8 expressing PD-1, JCV-specific T cell response and JCV DNA decay in pts survivor (A) and died (B).

### 337 INTRANASAL INSULIN IMPROVES ATTENTION AND MEMORY IN PEOPLE WITH HIV



Anne D. Yacoub<sup>1</sup>, Richard L. Skolasky<sup>1</sup>, Richard T. Moxley<sup>1</sup>, Justin McArthur<sup>1</sup>, Leah Rubin<sup>1</sup>, Norman D. Haughey<sup>1</sup>, Ned Sacktor<sup>1</sup>

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Despite suppression of HIV replication with antiretroviral therapies (ART), cognitive impairment (CI) remain prevalent in virally suppressed people with HIV (VS-PWH). Although the precise mechanisms for these residual CI are not fully understood, there is considerable evidence that brain energy metabolism is progressively impaired in VS-PWH. We hypothesized that intranasal insulin (INI) would enhance brain energetics in VS-PWH with consequent improvements in cognition.

**Methods:** In a randomized, double-blind, placebo-controlled study, 21 non-diabetic VS-PWH with mild-to-moderate CI were randomized to receive INI (20 IU/day/nare) or placebo. Participants completed standardized neuropsychological (NP) tests at baseline, 12, and 24 weeks. Demographically adjusted Z-scores were created for each outcome using the best available norms. Primary outcomes included Global Deficit Score (GDS), NPZ-8, and performance on individual NP tests. A series of mixed-effects regressions were conducted to examine the change in cognitive performance over 24 weeks as a function of Treatment Group. Models were adjusted for depressive symptoms.

**Results:** Of the 45 candidates screened, 21 met criteria for the study; top reasons for exclusion were insufficient CI (n=10) and current illicit drug use (n=8). No serious study-related adverse events were reported. Six participants discontinued the study early due to naso-pharyngeal irritation (n=3), non-compliance (n=2), and unrelated medical illness (n=1). There were no significant treatment group differences at baseline on any NP outcome (p>.05 for all comparisons; Student's t-test). A mixed effects regression of GDS over time with cross-product between INI and time demonstrated a significant treatment group effect (p.029) with improved GDS in the INI group at 12 and 24-weeks compared with placebo. Improvements on individual NP tests were apparent on measures of verbal memory (HVLt-R delayed free recall, p=.028) between baseline and 24-weeks, on visual memory (Rey delayed recall, p=.002) and attention (Trail Making Test-Part A, p=.006) between baseline and 12-weeks in the INI group compared to placebo. There were no Treatment Group differences over time on the NPZ-8.

**Conclusion:** In this pilot study, INI improved performance on NP tests related to memory and attention in VS-PWH. These findings warrant further investigation of intranasal insulin as a cognitive enhancer in VS-PWH.

### 338 STATIN USE AND COGNITIVE PERFORMANCE IN THE MULTICENTER AIDS COHORT STUDY

Deanna Saylor<sup>1</sup>, Samantha A. Molsberry<sup>2</sup>, Eric C. Seaberg<sup>1</sup>, Yu Cheng<sup>3</sup>, Andrew Levine<sup>4</sup>, Eileen Martin<sup>5</sup>, Cynthia Munro<sup>1</sup>, Frank Palella<sup>6</sup>, James Becker<sup>3</sup>, Ned Sacktor<sup>1</sup>

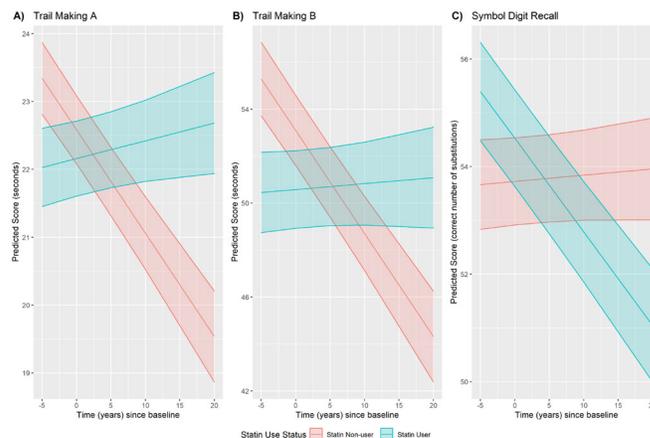
<sup>1</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>4</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>5</sup>Rush University, Chicago, IL, USA, <sup>6</sup>Northwestern University, Evanston, IL, USA

**Background:** Cardiovascular and cerebrovascular ischemic disease risk factors are associated with cognitive impairment in HIV seropositive individuals. Hypercholesterolemia, one such risk factor, is often treated with statin medications. Statin medications have both lipid lowering effect and anti-inflammatory properties, can improve endothelial function, and enhance dynamic blood flow in cerebral small vessels, which could potentially benefit cognitive function.

**Methods:** Using data from 1,407 participants in the Multicenter AIDS Cohort Study who either ever or never initiated statins, we explored the relationship between statin use and cognitive performance over time. Neuropsychological tests that were considered include: Trail Making A and B, Symbol Digit Recall, Grooved Pegboard dominant and non-dominant hands, Stroop interference, word, and color task, Rey Auditory Verbal Learning total score, and CALCAP simple reaction task 1, complex reaction task 3, and simple reaction task 4. Multivariable-adjusted linear regression analyses were estimated to determine the association between ever statin initiation and cognitive test performance at the visits prior to and post statin initiation. Longitudinal linear mixed-effects models were estimated to determine the relationship between statin use (ever or current) and cognitive test performance over time.

**Results:** After adjusting for potential confounders, statin initiation was not significantly associated with performance on any neuropsychological test either at the last test completion prior to statin initiation or for the first test completion after statin initiation. Longitudinally, statin use was strongly associated with cognitive test performance such that statin initiators tended to have, on average, a faster rate of cognitive test performance decline. HIV-serostatus did not significantly modify our results for the majority of cognitive tests that were explored.

**Conclusion:** After adjusting for confounders, cognitive test performance did not markedly differ between statin initiators and non-initiators at time proximal to initiation, but, longitudinally, statin initiators' test performance declined more quickly. HIV-serostatus did not modify these results.



### 339 REVERSIBILITY OF SLEEP DISTURBANCES AFTER SWITCHING FROM DTG/3TC/ABC TO DRV/C/FTC/TAF

Ignacio Perez-Valero<sup>1</sup>, Sara De La Fuente<sup>2</sup>, Rafael Mican<sup>1</sup>, María Novella Mena<sup>3</sup>, Miguel Górgolas<sup>4</sup>, Jesús Troya<sup>5</sup>, María Lagarde<sup>6</sup>, Alberto Diaz De Santiago<sup>2</sup>, Carmen Busca<sup>1</sup>, Pablo Ryan<sup>7</sup>, Beatriz Alvarez<sup>8</sup>, Cristina Hernandez Gutierrez<sup>8</sup>, Adriana Pinto-Martinez<sup>6</sup>, Alfonso Cabello Úbeda<sup>4</sup>, for the GESIDA 10418 - Detox Study Group

<sup>1</sup>La Paz University Hospital, Madrid, Spain, <sup>2</sup>Hospital Puerta de Hierro, Madrid, Spain, <sup>3</sup>University of Alcalá, Alcalá de Henares, Spain, <sup>4</sup>Fundacion Jimenez Diaz, Madrid, Spain, <sup>5</sup>Hospital Universitario Infanta Leonor, Madrid, Spain, <sup>6</sup>Hospital Universitario 12 de Octubre, Madrid, Spain, <sup>7</sup>Infanta Leonor Hospital, Madrid, Spain, <sup>8</sup>Hospital Universitario Príncipe de Asturias, Madrid, Spain

**Background:** Evidence supports switching DTG/3TC/ABC in patients complaining about insomnia. However, there is unknown if the benefit observed could also apply to non-complaining patients displaying sleep disturbances in self-reported questionnaires used as screening tools, such as the Pittsburgh sleep quality index (PSQI).

**Methods:** We designed the DETOX study, as an open label, randomized (1:1), multicenter, pilot clinical trial, to evaluate the reversibility of sleep disturbances detected with the PSQI in well-suppressed patients on DTG/3TC/ABC (>12 weeks) not complaining of insomnia. Participants with a PSQI >5 were randomized either to switch to DRV/c/FTC/TAF for 8 weeks (arm 1) or either to continue 4 weeks on DTG/3TC/ABC and then switch to DRV/c/FTC/TAF for 8 weeks (arm 2). Every 4 weeks, participants self-reported using the PSQI, the Hospital Anxiety & Depression Scale (HADS) and a questionnaire exploring about 11 neuropsychiatric adverse events (AE). Raw scores on PSQI and HADS, along with an average score from adding the grade of each neuropsychiatric AE, were normalized (0-100). Then we compared changes at week 4 (between study arms) and after participants completed 4 and 8 weeks on DRV/c/FTC/TAF. Additional analyses included virological outcomes.

**Results:** The study included 72 participants (arm 1: n=37; arm 2: n=35). Both arms had similar baseline characteristics. Three discontinued prematurely before week 4 (arm 1: none; arm 2: 1 COVID-19, 1 loss of follow up (LFU) and 1 consent withdrawal). At week 4, we observed significant improvements (arm 1 vs. arm 2) in PSQI (mean change±SD: 11.5±10.2 vs. 0.6±8.9; p<0.001), HADS anxiety scale (14±16.9 vs. 1.9±15.6; p=0.003) and AE (13.7±13.3 vs. 1.3±8.6; p<0.001) scores. Sixty-nine participants switched to DRV/c/FTC/TAF: 37 at baseline (arm 1) and 32 at week 4 (arm 2). All except 3 who discontinued prematurely (2 LFU and 1 due to AE nausea) completed 8 weeks of follow up.

Pooled analysis showed significant improvements in most neuropsychiatric scores and symptoms (table), with no virologic failures reported. After switching to DRV/c/FTC/TAF, 26 participants (37.7%) reported any AE (all grade 1-2). Most common AE were headache (7.2%) and dyslipidemia (7.2%).

**Conclusion:** Sleep disturbances detected through self-reported screening tools seem to be associated with patients on DTG/3TC/ABC not complaining of insomnia. These disturbances, among other neuropsychiatric symptoms such as anxiety or depression, could improve after switching to DRV/c/FTC/TAF.

**TABLE: Changes in CNS-related scores and symptoms at week 4 and 8 after switching from DTG/3TC/ABC to DRV/c/FTC/TAF**

|   | Baseline<br>(Before switching<br>to DRV/c/FTC/TAF)<br>(n=69) | Week 4 after<br>switching to<br>DRV/c/FTC/TAF<br>(n=67) | Week 8 after<br>switching to<br>DRV/c/FTC/TAF<br>(n=65) | P Value |
|---|--|---|---|---------|
| <b>CNS-related adverse events score, mean±SE</b>                          | 26.9±2   | 13.7±1.5  | 9.3±1.2   | <0.001  |
| <b>Hospital Anxiety and depression scale (Anxiety subscale), mean±SE</b>  | 36.8±2.3   | 26.1±2.1  | 22.2±2.1  | <0.001  |
| <b>Hospital Anxiety and depression scale Depression subscale, mean±SE</b> | 23.0±2.0   | 16.9±1.7  | 16.0±1.9  | 0.002   |
| <b>Pittsburg sleep quality index, mean±SE</b>                             | 36.9±1.3   | 27.6±1.6  | 21.5±1.5  | <0.001  |
| <b>Moderate to severe CNS-related adverse events (grade 2-3 vs. 0-1)</b>  |  |   |   |         |
| Headache, n (%)   | 9 (13)   | 7 (10.4)  | 6 (9.2)   | 0.747   |
| Abnormal dreams, n (%)  | 21 (30.4)  | 3 (4.5)   | 1 (1.5)   | <0.001  |
| Dizziness, n (%)  | 7 (10.1)   | 3 (4.4)   | 0 (0)   |         |
| Asthenia, n (%)   | 24 (34.8)  | 12 (18.2)   | 7 (10.8)  | 0.005   |
| Insomnia, n (%)   | 44 (63.8)  | 15 (22.4)   | 4 (6.2)   | <0.001  |
| Impaired concentration, n (%)   | 19 (27.5)  | 3 (4.5)   | 3 (4.6)   | <0.001  |
| Aggressive mood, n (%)  | 25 (36.2)  | 12 (17.9)   | 6 (9.2)   | 0.001   |
| Anxiety, n (%)  | 18 (26)  | 6 (9)   | 5 (7.7)   | 0.006   |
| Depression, n (%)   | 11 (15.9)  | 6 (8.9)   | 4 (6.2)   | 0.170   |

\* CNS: Central nervous system. SE: Standard Error.

**340 STABLE IMPROVEMENT IN DEPRESSION 6 YEARS AFTER ART INITIATION DURING ACUTE HIV**

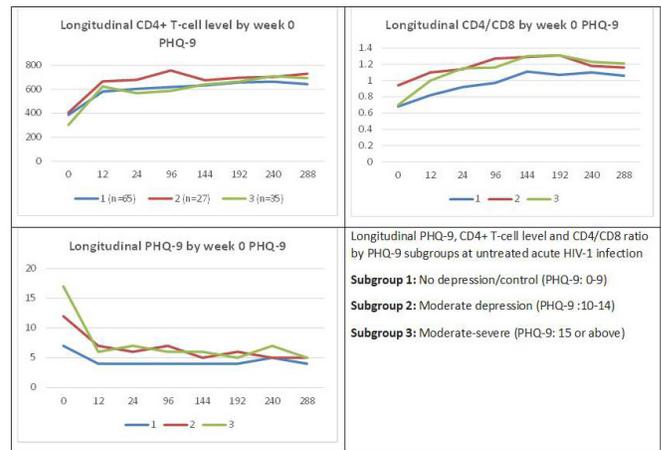
**Phillip Chan<sup>1</sup>**, Eugene Kroon<sup>1</sup>, Donn J. Colby<sup>1</sup>, Carlo Sacdalan<sup>1</sup>, Somchai Sreepleanjan<sup>1</sup>, Suteeraporn Pinyakorn<sup>2</sup>, Somporn Tipsuk<sup>1</sup>, Nitiya Chomchey<sup>1</sup>, Sandhya Vasan<sup>3</sup>, Victor Valcour<sup>4</sup>, Jintana Ananworanich<sup>5</sup>, Robert Paul<sup>6</sup>, Nittaya Phanuphak<sup>1</sup>, Serena S. Spudich<sup>7</sup>, for the RV254 Study Team  
<sup>1</sup>SEARCH, Bangkok, Thailand, <sup>2</sup>US Military HIV Research Program, Bethesda, MD, USA, <sup>3</sup>US Military HIV Research Program, Silver Spring, MD, USA, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA, <sup>5</sup>University of Amsterdam, Amsterdam, Netherlands, <sup>6</sup>University of Missouri St Louis, St Louis, MO, USA, <sup>7</sup>Yale University, New Haven, CT, USA

**Background:** In individuals with acute HIV-1 infection (AHI) in Bangkok, Thailand, overt depression symptoms are common but improve by 6 months after prompt initiation of antiretroviral therapy (ART). It is unclear if this improvement in mood symptoms is durable up to six years following ART started during AHI.

**Methods:** RV254 cohort participants initiated ART at a median=0 [IQR 0-1] days after AHI diagnosis (Fiebig I-V) and completed the 9-item Patient Health Questionnaire (PHQ-9, score 0-27) for depression symptoms and the Distress Thermometer (DT) for anxiety/stress (score 0-10) at untreated AHI (baseline), weeks 12, 24, 96 and every 48 weeks thereafter. This analysis included participants who maintained suppressive ART over 288 weeks of follow-up, defined by the absence of plasma HIV RNA >400 cps/ml. Week 288 PHQ-9 scores, CD4+ T cell counts, and CD4/CD8 levels were compared based on baseline PHQ-9 scores (No depression: ≤9; moderate depression: 10-14; moderate-severe depression: ≥15).

**Results:** By Sep 2020, 243 participants reached week 288 post-ART. 15 withdrew from the cohort; 17 failed HIV control criteria; 54 were co-enrolled into analytical treatment interruption studies; 30 did not have paired baseline and week 288 records. Of the remaining 127 participants (95% male, median age 28 years), the median PHQ-9 and DT scores at baseline were 9 [IQR 7-16] and 6 [IQR 3.2-7.5] respectively. The rates of moderate and moderate-severe depression symptoms at baseline were 21% and 27%, respectively. Median PHQ-9 and DT scores improved post-ART to subclinical levels by week 24. The rates of moderate and moderate-severe depression symptoms were stable at ≈10% and ≤4% after week 96. Baseline PHQ-9 score correlated with the score at week 288 (p<0.001). At baseline, participants with PHQ-9≥15 had higher plasma HIV RNA (p=0.011) and frequency of acute retroviral syndrome (p=0.043) than the rest of the group (PHQ-9<15). Participants with PHQ-9≥15 at baseline trended towards higher PHQ-9 scores than no depression group at week 288 (5 [IQR 2-8] vs. 4 [IQR 1-6], p=0.083), but had a non-inferior immune recovery in CD4+ T-cell and CD4/CD8 levels (Figure 1).

**Conclusion:** in those who maintain viral suppression after ART initiation during AHI, depression symptoms remain stably improved at 6 years. While overall, PHQ-9 score at 6 years correlates with baseline score during AHI, moderate-severe depression symptoms during AHI do not portend durable depression symptoms or impaired immunologic recovery after long-term ART.



**341 HIV REPLICATION IN THE CNS IS ASSOCIATED WITH NEUROCOGNITION AND DEPRESSION PRE-ART**

**Sarah B. Joseph<sup>1</sup>**, Jessica Keys<sup>1</sup>, Leah Rubin<sup>2</sup>, Deanna Saylor<sup>2</sup>, Gertrude F. Nakigozi<sup>3</sup>, Noeline Nakasujja<sup>4</sup>, Thomas Quinn<sup>5</sup>, Sabrina Clark<sup>1</sup>, Oliver Laeyendecker<sup>5</sup>, Steven J. Reynolds<sup>5</sup>, Maria Wawer<sup>2</sup>, Robert Paul<sup>6</sup>, Alyssa Vecchio<sup>1</sup>, Ronald Swanstrom<sup>1</sup>, Ned Sacktor<sup>2</sup>

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>3</sup>Rakai Health Sciences Program, Kalisizo, Uganda, <sup>4</sup>Makerere University, Kampala, Uganda, <sup>5</sup>National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, <sup>6</sup>Missouri Institute of Mental Health, St Louis, MO, USA

**Background:** People with HIV (PWH) experience more neurocognitive impairment and depression than uninfected individuals, particularly in resource-limited settings. However, initiating ART often returns neurocognition and depression to levels observed for uninfected people. Here we test the hypothesis that neurocognition and depression are substantially impacted by HIV replication in the CNS, beyond the effects of systemic replication or stigma related stress.

**Methods:** We successfully sequenced viral populations in cerebrospinal fluid (CSF) and blood collected from 50 ART-naive PWH enrolled in the Rakai Neurology Cohort Study (RNCS; sequencing attempted for 169 PWH). Viral RNA was isolated from plasma and CSF and Illumina MiSeq deep sequencing with Primer ID was used to sequence env V1-V3. Identification of a CSF viral lineage that was genetically distinct from HIV in the blood (i.e. compartmentalized) was evidence of sustained viral replication in the CNS. The viral burden of HIV replication in the CNS was estimated as the Compartmentalized CSF Viral Load (CCVL = the percent of CSF-derived sequences that are CSF-specific \* CSF viral load). All 50 individuals completed a neuropsychological test battery, assessment of depressive symptoms (CES-D) and self-assessment of function (PAOFI).

**Results:** The mean CCVL in this cohort of 50 was 3.5 log<sub>10</sub> RNA cp/ml (SD=1.72). Higher CCVL was associated with slower processing speed (p<0.001), lower global cognition (total z-score, p=0.049), a lower self-assessment of function (PAOFI, p=0.044) and greater depression (CES-D, p=0.003). Further, the relationship between CCVL and depression (OR: 2.9 CI: 1.2-7.2) remained significant even after adjusting for BMI, sex at birth, daily alcohol use, and pre-ART plasma viral load. Similarly, the components used to calculate CCVL were not independently associated with depression or neurocognition.

**Conclusion:** A measure of the viral burden in the CNS due to local replication (i.e. CCVL) was more strongly associated with neuropsychiatric outcomes pre-ART than CSF or plasma viral load. These findings suggest that cognitive function and depression in ART-naive PWH is not only due to global changes in the immune and/or inflammatory environment, but may be directly related to compartmentalized replication in the CNS. These findings provide additional

support for the need to fully suppress viral replication in the CNS during ART and the need to better understand the biology of HIV replication in the CNS.

#### 342 CELL-TYPE SPECIFIC GENOMICS AND TRANSCRIPTOMICS OF HIV IN THE BRAIN

Amara Plaza-Jennings<sup>1</sup>, Callan O'Shea<sup>1</sup>, Benjamin K. Chen<sup>1</sup>, Susan Morgello<sup>1</sup>, Lotje De Witte<sup>1</sup>, Shahram Akbarian<sup>1</sup>

<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA

**Background:** Characterization of organ-specific reservoirs is critical as we look toward a functional cure for HIV. Due to the lack of reliable brain biomarkers of persistence and the difficulty of studying the human brain in vivo, there have not been in depth molecular studies of the brain reservoir. Viral integration is a key step in establishing the reservoir. Studies in T-cells have shown that HIV preferentially integrates into active, highly expressed regions of the genome; however, integration and its effects have not been studied in the brain.

**Methods:** Neuronal and glial nuclei were isolated using fluorescence activated nuclei sorting from postmortem frontal cortex samples provided by the Manhattan HIV Brain Bank. Integration site sequencing libraries were generated for neurons and glia for a total of 27 brains (n= 6 HIV-, n= 15 HIV+ non-encephalitis [ HIV+], n= 6 HIV encephalitis [HIVE]). A subset of samples were submitted for 10X Chromium single nucleus RNA-sequencing (snRNA-seq).

**Results:** We identified 1,279 integration sites (IS), predominantly from the glial cell fraction of HIVE cases. Glial IS were found preferentially in introns, gene dense regions, and active regions of the genome as marked by H3K37ac. Glial IS showed a stronger preference for integration into SINE repeat elements than T-cell IS and contain a significantly lower proportion of clonal (5% v 18%, p<0.0001) and recurrent (13% v 30%, p<0.0001) IS. Notably not all IS were found to be in genes that were highly expressed in HIVE microglia by snRNA-seq, and genes that were targeted for recurrent integration were expressed at the same level as non-recurrent genes. Differential expression analysis revealed that microglia with active viral transcription have elevated expression of core markers of microglial activation and decreased expression of markers of proliferation.

**Conclusion:** We see evidence for glial-specific patterns of IS selection. CPSF6 and LEDGF, the two proteins involved in IS targeting in T-cells, are not highly expressed in microglia, raising the possibility that there may be different mechanisms of integration in the brain. snRNA-seq also revealed that there are changes in activation and proliferation specifically within those microglia with active viral transcription. These findings coupled with the low proportion of clonal integration sites found in glia indicate that HIV infected microglia do not proliferate.

#### 343 PREDICTIVE FACTORS FOR HIV-1 CSF ESCAPE IN NEUROCOGNITIVE IMPAIRMENT

Paraskevas Filippidis<sup>1</sup>, José Damas<sup>1</sup>, Benjamin Viala<sup>2</sup>, Frederic Assal<sup>3</sup>, Alexandra Calmy<sup>3</sup>, Philip Tarr<sup>4</sup>, Tobias Derfuss<sup>5</sup>, Michael Oberholzer<sup>6</sup>, Ilijas Jelcic<sup>7</sup>, Thomas Hundsberger<sup>8</sup>, Leonardo Sacco<sup>9</sup>, Matthias Cavassini<sup>1</sup>, Renaud Du-Pasquier<sup>1</sup>, Katharine E. Darling<sup>1</sup>

<sup>1</sup>Lausanne University Hospital, Lausanne, Switzerland, <sup>2</sup>Centre Hospitalier Alpes Léman, Contamine-sur-Arve, France, <sup>3</sup>University Hospital of Geneva, Geneva, Switzerland, <sup>4</sup>Kantonsspital Bruderholz, Basel, Switzerland, <sup>5</sup>University Hospital Basel, Basel, Switzerland, <sup>6</sup>Bern University Hospital, Bern, Switzerland, <sup>7</sup>University Hospital Zurich, Zurich, Switzerland, <sup>8</sup>St Gallen Cantonal Hospital, St Gallen, Switzerland, <sup>9</sup>L'Hospitalet Clinical Laboratory, Barcelona, Spain

**Background:** Among people with HIV (PWH) enrolled in the Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study, we have observed a neurocognitive impairment (NCI) prevalence of 40%. In the current study, we examined the characteristics of patients with HIV viral escape in the cerebrospinal fluid (CSF).

**Methods:** We pooled data from NAMACO study participants and from patients attending a neuro-HIV platform in Switzerland. The NAMACO study is an ongoing, prospective, longitudinal, multicentre study of aging (≥45 years old) PWH enrolled in the Swiss HIV Cohort Study (SHCS). NAMACO participants in whom HIV-related NCI is diagnosed are invited to pursue investigations with a neurological examination, brain MRI and CSF analysis. The neuro-HIV platform is a multi-disciplinary full outpatient assessment at Lausanne University Hospital for PWH of any age, enrolled in the SHCS or not, in whom NCI is suspected. We analysed the demographic, clinical, immunological, neurocognitive and radiological characteristics of PWH who underwent lumbar puncture (LP) as

part of the NAMACO study or the neuro-HIV platform between 1 March 2011 and 30 April 2019. CSF viral escape was defined as 1) the presence of quantifiable HIV RNA in the CSF at any level when plasma HIV RNA was suppressed or 2) CSF HIV RNA greater than plasma HIV RNA when the latter was detectable.

**Results:** Of 1166 PWH assessed, 287 underwent LP. The majority had suppressed plasma HIV RNA. CSF viral escape was observed in 29 patients (10%) of whom 18 (62%) had suppressed plasma HIV RNA and 11 (38%) had detectable plasma HIV RNA. Characteristics of patients were comparable whether they had CSF viral escape or not, including demographic profile, cardiovascular and metabolic comorbidities, time since HIV diagnosis (12 vs 16 years, p=0.4), median current CD4 count (558/mm<sup>3</sup> vs 611/mm<sup>3</sup>, p=0.1) and median CD4 nadir (170/mm<sup>3</sup> vs 171/mm<sup>3</sup>, p=0.7), antiretroviral CSF Penetration-Effectiveness score (7 vs 8 points, p=0.2), neurocognitive diagnosis based on Frascati criteria and presence of MRI abnormalities.

**Conclusion:** In this large pooled sample of PWH assessed for NCI, CSF viral escape occurred in 10% of patients. Patients with CSF viral escape presented no significant demographic, clinical, immunological, neurocognitive or radiological differences compared to patients without CSF escape. We conclude that LP remains the only reliable means of diagnosing HIV-1 escape in the CSF.

#### 344 ELUCIDATING THE ORIGINS OF HIV-1 IN THE CEREBROSPINAL FLUID

Olivia D. Council<sup>1</sup>, Laura Kincer<sup>1</sup>, Sarah B. Joseph<sup>1</sup>, Susan Morgello<sup>2</sup>, Benjamin B. Gelman<sup>3</sup>, Ronald Swanstrom<sup>1</sup>

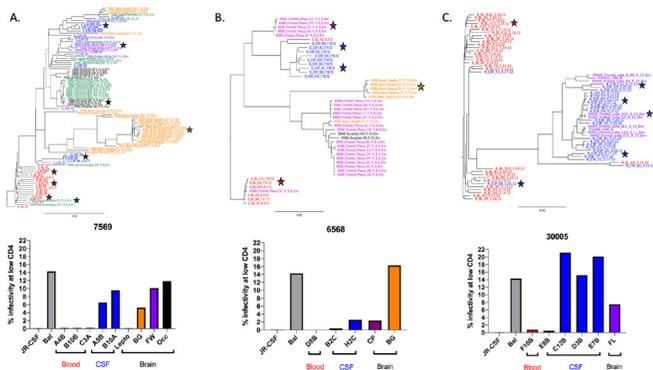
<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>3</sup>University of Texas at Galveston, Galveston, TX, USA

**Background:** HIV-1 infection of the CNS has implications for both treatment and cure strategies. Putative CNS reservoirs would likely be linked to sites of viral replication. HIV-1 RNA in the cerebrospinal fluid (CSF) can occasionally be genetically distinct from virus in the blood, indicating that the CNS can serve as a site for independent viral replication. However, the source of HIV-1 in the CSF from within the CNS is unknown and thus the sites of viral replication, and sites of potential reservoirs, remain to be determined.

**Methods:** Paired blood, CSF, and autopsy tissue samples from multiple brain regions were obtained from 5 participants enrolled in the NNTC. These individuals were diagnosed with HIV-associated dementia, and no participant was taking ART at the time of death. HIV-1 genomes were extracted from blood/CSF (RNA) and brain tissues (DNA). The burden of HIV-1 DNA in various regions of the brain was quantified using ddPCR. Single genome amplification was performed on blood, CSF, and brain tissue samples in order to obtain full-length HIV-1 env sequences. Pseudotyped reporter viruses were generated from a total of 32 env genes cloned from 5 participants (22 from brain or CSF and 10 from blood plasma) and used in single-cycle entry assays to assess entry phenotype.

**Results:** In this cohort of 5 untreated people with HAD, the burden of HIV-infected cells varied across different regions of the brain, ranging from below the limit of detection to over 100,000 copies per million cells. In 3/5 participants, brain- and CSF-derived sequences were compartmentalized from blood-derived sequences. Overall, viral diversity present in the CSF represents much of the viral diversity found in the brain, but brain-specific lineages were also observed. In 2/5 participants, blood, CSF, and brain-derived sequences were intermingled, suggestive of a lack of independent viral evolution within the CNS. Compartmentalized CSF/brain Env proteins mediated efficient entry into cells expressing low densities of CD4 (M-tropic), whereas equilibrated Env proteins did not (R5 T-tropic).

**Conclusion:** In this small, pilot study we observed that the viral diversity present within the CSF represents much, but not all, of the viral diversity present within various regions of the brain. Indeed, viral diversity and entry phenotype can vary across different regions of the brain in the same participant. Altogether, the CSF captures the majority of the genotypic and phenotypic properties of HIV-1 in the CNS of individuals with HAD.



**Figure 1.** Compartmentalized, brain-derived HIV-1 envelopes are able to efficiently enter cells expressing low densities of CD4. A-C) Top: Neighbor-joining phylogenetic trees containing blood- (red), CSF- (blue) and brain (leptomeninges: green, frontal lobe: purple, basal ganglia: orange, and occipital lobe: black) HIV-1 envelope sequences. Stars represent sequences used in entry assay experiments. Bottom: Single-cycle infectivity assay. JR-CSF and Bal are T cell-tropic and macrophage-tropic controls, respectively. A) participant 7569. B) participant 6568. C) participant 30005.

**345 PEMBROLIZUMAB TREATMENT IS ASSOCIATED WITH DECREASED CELL-ASSOCIATED HIV DNA IN CSF**

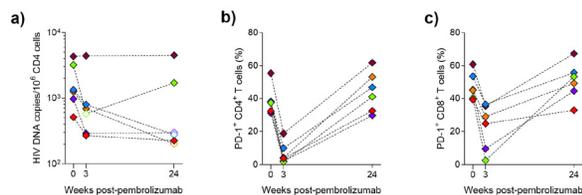
**Cynthia McMahan<sup>1</sup>**, Liliana Pérez<sup>2</sup>, Elizabeth Horne<sup>3</sup>, Jong Shin<sup>4</sup>, Ulisses Santamaria<sup>5</sup>, Bryan R. Smith<sup>1</sup>, Avindra Nath<sup>1</sup>, Eli A. Boritz<sup>2</sup>, Lauren B. Reoma<sup>1</sup>  
<sup>1</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, <sup>2</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>3</sup>Duke University School of Medicine, Durham, NC, USA, <sup>4</sup>National Institute on Aging, Baltimore, MD, USA, <sup>5</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA

**Background:** Pembrolizumab is a monoclonal antibody against programmed cell death protein 1 (PD-1) approved to treat many forms of cancer. PD-1 is a negative regulator of T cell responses and its expression on T cells is upregulated in chronic HIV infection, even when infection is well-controlled by antiretroviral therapy (ART). PD-1 blockade may be a promising target for future studies of viral clearance. Identifying and monitoring the HIV reservoir, in elusive locations such as the central nervous system (CNS), is a crucial step in any viral clearance strategy. We evaluated the effects of pembrolizumab on immunologic markers in the blood and cerebrospinal fluid (CSF) to test the hypothesis that this treatment may be used to target HIV reservoirs in the CNS.

**Methods:** HIV+ participants (n=6) were given a single dose of pembrolizumab in this phase I proof-of-concept study. CSF was collected at baseline, 3, and 24 weeks after dosing. Safety and tolerability were also monitored at these timepoints. All participants had a CD4 count of >350 cells/μL at baseline and were on ART with a plasma HIV RNA ≤ 40 copies/mL for at least 12 months prior to starting the trial. Multiparameter flow cytometry was obtained from 18.5mL of fresh CSF. HIV-1 DNA was quantified by limiting dilution PCR targeting a region of env.

**Results:** Pembrolizumab administration was associated with a sharp decrease in cell-associated (CA)-HIV DNA levels in the CSF. CA-HIV DNA levels were a median of 46.1% lower at week 3 when compared to pre-treatment levels. At week 24, levels remained similar, a median of 7.17% lower when compared to week 3 (Fig. 1a). As expected, the proportion of CSF PD-1+ CD4+ and CD8+ T cells declined between baseline and week 3 and rebounded back to baseline levels at week 24 (Fig. 1b-c). Expression of other immune checkpoints (PD-L1, TIGIT, LAG3) appeared to be independent of PD-1 expression at week 24 (data not shown). Adverse events (AE) were minimal, with only one grade 2 AE of hypertriglyceridemia, and no grade 3 AEs.

**Conclusion:** A single dose of pembrolizumab was well-tolerated and effectively targeted PD-1 in the CSF. In most participants, pembrolizumab was associated with a reduction in CA-HIV DNA, highlighting its potential role in reservoir targeting studies. In the CNS, CA-HIV DNA is of particular interest due to its association with worse cognitive performance.



**Figure 1.** Pembrolizumab reduces cell-associated HIV DNA in cerebrospinal fluid (a), and measurements of PD-1 expression on T cells (b-c) confirm its effectiveness in the central nervous system.

**346 NEUROMODULATORY EFFECTS OF SARS-CoV-2 ON THE BLOOD-BRAIN BARRIER**

**Erin Clough<sup>1</sup>**, Lee Chavis<sup>1</sup>, Jessica L. Reynolds<sup>1</sup>, Supriya D. Mahajan<sup>1</sup>  
<sup>1</sup>SUNY at Buffalo, Buffalo, NY, USA

**Background:** Autopsies of the COVID-19 patients, show presence of SARS-CoV-2 in the brain endothelium, cerebrospinal fluid, glial cells, and neuronal tissue and emerging clinical data from the current pandemic suggests that ~40% of the patients with COVID-19 developed neurological symptoms. We examined the effect of SARS-CoV-2 RBD spike protein and heat inactivated SARS-CoV-2 on Blood barrier barrier (BBB) integrity using a well validated 2D in-vitro Blood brain barrier model, and on the expression levels of tight junction proteins (TJP) that are key to BBB permeability and function.

**Methods:** Our experimental paradigm included treating primary human BMVEC (Cat# ACBRI-376) with recombinant SARS-CoV-2 Spike protein ( BEI Resources Inc) for 24-48 hrs, followed by examining ACE2 receptor expression by immunofluorescent staining, quantification of levels of pro-inflammatory cytokines in culture supernatants using BioLegend's LEGENDplex™ bead-based immunoassay. Additionally, we examined the effects of SARS-CoV-2 on BBB integrity using a well validated 2D in-vitro BBB model and modulation of TJ protein gene expression levels using real time quantitative PCR.

**Results:** Our data shows that primary human BMVEC expressed the ACE2 receptor and that treatment with SARS-CoV-2 spike protein resulted in a significant increase in ACE 2 receptor expression by BMVEC. We observed a significant increase in the levels of pro-inflammatory cytokines such as TNF-α (p<0.01), IL-6 (p<0.0001), IL-10 (p<0.05), IL-23 (p<0.05) and IL-33 (p<0.01) in BMVEC treated with SARS-CoV2 spike protein compared to the untreated controls. BBB integrity which was measured using the transendothelial electrical resistance (TEER) across membrane showed an ~ 30% (p<0.05) decrease in TEER in BBB treated with SARS-CoV2 spike protein as compared to the untreated control, and the functional translational of this effects was evident by the SARS-CoV2 induced decrease in TJP expression. Our data showed that SARS-CoV-2 treatment resulted in a decrease in the gene expression of TJPs- ZO-1 (52%;p<0.05), ZO-2 (92%;p<0.001), Claudin-5 (97%;p<0.001) and JAM-2 (45%;p<0.05) as compared to the untreated controls.

**Conclusion:** BMVEC have a paracrine-autocrine role in maintaining CNS homeostasis and that the SARS-CoV2 associated endothelial cell dysfunction precludes the neuropathology associated with SARS-CoV2 that is observed in COVID-19 infected patients. Potentially, anti-cytokine based therapeutics may be effective in treating patients with COVID-19 associated neurological disease.

**347 DIMETHYL FUMARATE REDUCES BRAIN OXIDATIVE STRESS AND INFLAMMATION IN SIV INFECTION**

**Yoelvis Garcia-Mesa<sup>1</sup>**, Patricia Vance<sup>1</sup>, Analise L. Gruenewald<sup>1</sup>, Rolando Garza<sup>1</sup>, Cecily Midkiff<sup>2</sup>, Xavier Alvarez-Hernandez<sup>2</sup>, David J. Irwin<sup>1</sup>, Alexander J. Gill<sup>1</sup>, Dennis L. Kolson<sup>1</sup>

<sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Tulane National Primate Research Center, Covington, LA, USA

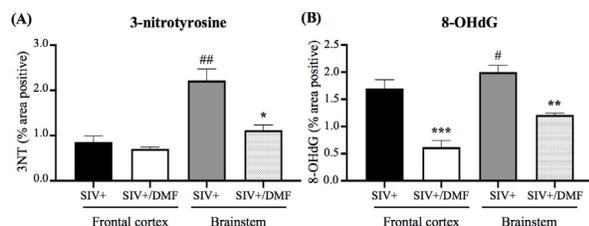
**Background:** Dimethyl fumarate (DMF), an FDA-approved, anti-inflammatory, antioxidant neuroprotective drug acts in part through antioxidative gene induction. For testing as an HIV neuroprotectant, we had shown that DMF, with or without cART, increases antioxidant enzyme expression and reduces excitotoxin release from HIV-infected macrophages (HIV/SIV brain reservoir). We hypothesized that DMF treatment of SIV-infected macaques would induce brain antioxidant responses and reduce oxidative stress and neuroinflammation.

**Methods:** Ten SIV-infected CD8+ T cell-depleted rhesus macaques were studied. Six received DMF [feeding, physiological dosing ~7 mg/kg/d] starting 7d prior to SIVmac251 infection and through necropsy (40-118d). DMF metabolism in vivo was confirmed prior to infection (3 animals). We quantified SIV load, neurofilament light chain (NFL) in plasma and cerebrospinal fluid (CSF). In brain (11 regions), thymus, liver, and spleen we quantified: synaptic (PSD-95, synaptophysin, synapsin-1), axonal (NFL), astrocytic (GFAP), endothelial (VCAM-1, ICAM-1), and antioxidant enzymes (NQO1, GPX1, PRDX1, HO-1, 2). Frontal cortex (Fc) and brainstem (Bs) were stained for oxidative stress (8-OHdG/DNA, 3NT/proteins) and inflammation (HLA-DR, CD68). Statistical analyses were done by unpaired and paired t-test, and multivariate linear regression.

**Results:** Chronic daily DMF treatment associated with higher mean expression of NQO1 (p<0.01), PRDX1 (p<0.05), GPX1 (p<0.001), VCAM-1 (p<0.01), and ICAM-1 (p<0.01) in brain; and higher PRDX1 (p<0.01) and HO-2 (p<0.01) in spleen. DMF treatment reduced 8-OHdG and 3NT expression in Bs (p<0.01,

$p < 0.05$ , respectively) and 8-OHdG ( $p < 0.001$ ) and HLA-DR in Fc ( $p < 0.05$ ). There were no changes in NFL, PSD-95, GFAP or CD68 expression; and no changes in plasma or CSF NFL, SIV load, or hematologic parameters. One DMF-treated animal developed a diffuse lymphosarcoma and a jejunal B cell lymphoma (lymphocryptovirus), commonly associated with SIV infection.

**Conclusion:** Oral DMF treatment of SIV-infected rhesus macaques induces antioxidant enzyme expression while reducing DNA and protein oxidation and macrophage activation throughout vulnerable brain areas. A lack of adverse effects on SIV load, hematologic parameters, and CSF and plasma NFL levels suggests that DMF can safely induce potential neuroprotective brain responses despite severe immune deficiency. These results support the re-purposing of DMF for testing as a potential neuroprotective adjunct against HIV at all infection stages.



**DMF treatment reduces markers of oxidative stress in frontal cortex and brainstem of SIV-infected macaques. Brainstem shows higher amount of 3NT and 8-OHdG than frontal cortex. (A)** Quantification of 3NT-nitrosylated proteins. DMF treatment reduces 3NT in brainstem (statistical analysis by Student's unpaired t test, \* $p < 0.05$ ). 3NT-nitrosylated proteins are higher in brainstem than in frontal cortex (statistical analysis was done using Student's unpaired t test, \*\* $p < 0.01$ ). **(B)** Quantification of 8-OHdG-oxidation of DNA. DMF treatment reduces 8-OHdG in both regions (statistical analysis by Student's unpaired t test, \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ). 8-OHdG DNA oxidation is higher in brainstem than in frontal cortex (statistical analysis by Student's unpaired t test, \* $p < 0.05$ ). Quantifications are expressed as percent of positive staining from all the area stained, and the mean  $\pm$  SEM.

### 348 GUT DYSBIOSIS IN PEOPLE WITH HIV WHO HAVE NEUROPATHIC PAIN

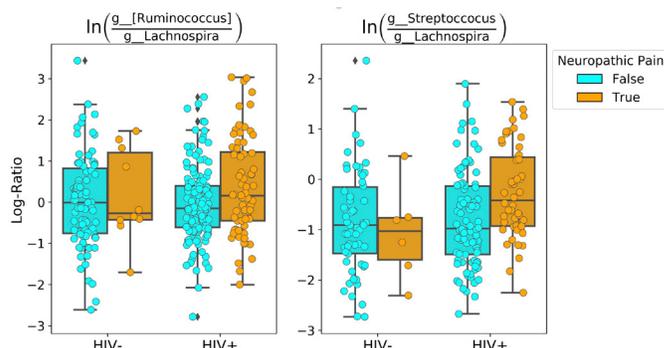
Ronald J. Ellis<sup>1</sup>, Robert K. Heaton<sup>2</sup>, Sara Gianella<sup>2</sup>, Gibraan Rahman<sup>1</sup>, Rob Knight<sup>2</sup>  
<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>University of California San Diego, San Diego, CA, USA

**Background:** Gut dysbiosis, defined as pathogenic alterations in the distribution and abundance of different microbial species, is associated with neuropathic pain in a variety of clinical conditions such as nerve trauma, but this has not been explored in the context of neuropathy in people with (PWH).

**Methods:** We assessed gut microbial diversity in PWH and people without HIV (PWoH), some of whom reported distal neuropathic pain (DNP). DNP was graded on a standardized, validated severity scale. The gut microbiome was characterized using 16S rRNA sequencing and diversity was assessed by phylogenetic tree construction. Songbird analysis was used to produce a multinomial regression model predicting counts of specific microbial taxa through metadata covariate columns.

**Results:** Participants were 267 PWH and 106 PWoH, 20.1% females, 45.3% nonwhite. Among PWH, median (interquartile range, IQR) nadir and current CD4 were 174 (21, 302) and 618 (448, 822) respectively; 90% were virally suppressed on antiretroviral therapy. PWH and PWoH did not differ with respect to microbiome diversity as indexed by Faith's phylogenetic diversity (PD). More severe neuropathic pain was associated with lower alpha diversity as indexed by Faith's PD ( $r = -0.158$ ;  $p = 0.0043$ ) in PWH, but not in PWoH. These relationships were not confounded by demographics or disease factors. In addition, the log-ratio of features identified at the genus level as [Ruminococcus] to Lachnospira was statistically significantly higher in PWH with DNP than in PWH without DNP (t-test,  $p = 0.007$ ). The Ruminococcus association is reported with note of the potential error in identification, as indicated by brackets. Furthermore, the log-ratio of Streptococcus features to Lachnospira features also was higher in PWH with DNP than in those without (t-test,  $p = 0.001$ ).

**Conclusion:** Our results, in combination with previous findings in other neuropathic pain conditions, suggest that gut dysbiosis, particularly reductions in diversity and relative increases in the ratios of Ruminococcus and Streptococcus to Lachnospira, may contribute to prevalent neuropathic pain in PWH. Two candidate pathways for these associations, involving microbial pro-inflammatory components and microbially-produced anti-inflammatory short chain fatty acids, are discussed. Future studies might test interventions to re-establish a healthy gut microbiota and determine if this prevents or improves neuropathic pain.



### 349 WITHDRAWN

### 350 PHENOTYPIC CHANGE OF MONOCYTES INDUCED BY PLASMA EXOSOMES FROM HIV(+) WOMEN WITH HAND

Bryan J. Collazo-Rodriguez<sup>1</sup>, Juan C. Medina<sup>1</sup>, Jaylene Alvarez<sup>1</sup>, Dariana Morales<sup>1</sup>, Cristhian Negron<sup>1</sup>, Yisel Cantres<sup>1</sup>, Elaine Rodriguez<sup>1</sup>, Valerie Wojna<sup>1</sup>, Yamil Gerena<sup>1</sup>

<sup>1</sup>University of Puerto Rico, San Juan, Puerto Rico

**Background:** Currently, an inflammatory monocyte subpopulation CD14+/CD16+ persists in peripheral blood of virologically suppressed HIV(+) individuals and plays a crucial role in the development of HIV-associated neurocognitive disorders (HAND). However, the factors responsible for the persistent changes in monocyte phenotypic profile are not yet well understood. Previously, we showed that plasma exosomes from HIV(+) women with HAND carry high levels of soluble insulin receptor, HIV-1 Tat, and reactive oxygen species. The influence of these exosomes in the phenotypic profile of HIV-uninfected monocytes has never been explored. In this study, we investigated if plasma exosomes from HIV(+) women induces a phenotypic change toward a CD14+/CD16+ subpopulation in HIV-uninfected monocytes.

**Methods:** The membrane of plasma exosomes (20 $\mu$ g) from HIV(-) women (controls) and HIV(+) women with Normal Cognition (NC) or HAND were labeled using PKH-67 Green Fluorescent Cell Linker Kit (30nM) prior to incubation with PBMCs (2.5x10<sup>5</sup> cells) from HIV(-) women donors at different times (1-48h). Exosome uptake levels and changes in the percentage of monocyte subpopulations were measured by flow cytometry, using PE/Cy7-anti-CD14 and Pacific Blue-anti-CD16 antibodies.

**Results:** Our results showed that: (1) Exosome uptake levels increased significantly in CD14+/CD16- ( $p = 7.8 \times 10^{-8}$ ) and CD14+/CD16+ ( $p = 2.6 \times 10^{-7}$ ) subpopulations exposed to exosomes from NC patients in a time-dependent manner, with a maximal response at 6h or 24h, respectively. (2) A similar response was observed in CD14+/CD16+ ( $p = 5.9 \times 10^{-9}$ ) subpopulation exposed to exosomes from HAND patients with a maximal response at 48h. (3) The percentage of CD14+/CD16- decreased significantly ( $p = 2.6 \times 10^{-13}$ ), whereas CD14+/CD16+ increased ( $p = 2.8 \times 10^{-13}$ ) in monocytes exposed to exosomes from NC patients in a time-dependent manner, with a maximal response at 24h. (4) The phenotypic changes (%) toward a CD14+/CD16+ ( $p = 5.2 \times 10^{-14}$ ) subpopulation were more rapid (maximal response at 12h) in monocytes exposed to exosomes from HAND patients when compared to NC (24h).

**Conclusion:** Our findings suggest that exosomes from plasma of HIV(+) patients differentially influence a phenotypic change to an inflammatory subset in HIV-uninfected monocytes. These findings could give new insights in the factors responsible for the monocytic activation and the cognitive impairment in HIV(+) patients to identify novel mechanisms and possible therapeutic targets.

### 351 COMPARATIVE ANALYSIS OF HUMAN MICROGLIAL MODELS FOR STUDIES OF HIV REPLICATION

Jason E. Hammonds<sup>1</sup>, Mohammad A. Rai<sup>2</sup>, Mario Pujato<sup>1</sup>, Christopher Mayhew<sup>1</sup>, Krishna Roskin<sup>1</sup>, Paul Spearman<sup>1</sup>

<sup>1</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, <sup>2</sup>University of Cincinnati, Cincinnati, OH, USA

**Background:** HIV associated neurocognitive disorders (HAND) cause significant morbidity and mortality despite the advent of highly active antiretroviral therapy. A deeper understanding of fundamental molecular mechanisms

underlying HIV neuropathogenesis in the central nervous system (CNS) will require relevant model systems. Microglia are resident myeloid cells of the brain that are readily infected by HIV and are likely to contribute to HAND. The purpose of this study was to define the most relevant microglial model systems for those working on HIV infection, replication, and pathogenesis in the CNS.

**Methods:** We evaluated two microglial model cell lines (C20, HMC3) and two sources of primary cell-derived microglia (monocyte-derived microglia [MMG] and induced pluripotent stem cell-derived microglia [iPSC-MG]) as model systems for studying HIV-microglia interactions. Cells were evaluated for relevant marker expression by flow cytometry and immunofluorescence microscopy. Gene expression analysis was performed and results compared between model systems and published microglial datasets.

**Results:** All four microglial model cells expressed typical myeloid and microglia-specific markers. Significant differences were observed upon gene expression profiling, however. MMG and iPSC-MG clustered closely with primary human microglial cells, while C20 and HMC3 exhibited marked differences. iPSC-MG and MMG expressed HIV-related genes in a manner closely resembling primary microglia. iPSC-MG and MMG were readily infected with R5-tropic HIV, while C20 and HMC3 required pseudotyping for infection. HIV replication dynamics and HIV-1 particle capture by Siglec-1 differed noticeably between MMG and iPSC-MG. In order to study HIV neuropathogenesis in a more CNS representative system, these findings are being extended to a three-dimensional (3D) iPSC-derived cerebral organoid model incorporating iPSC-MG. **Conclusion:** iPSC-MG and MMG were superior to transformed microglia cell lines in their similarity to authentic microglia, expression of HIV-relevant genes, and capacity to support HIV replication.

### 352 VALIDATION OF RAPID SEMIQUANTITATIVE LATERAL FLOW ASSAY FOR URINE TENOFOVIR

Derin Sevenler<sup>1</sup>, Sandy Dossantos<sup>1</sup>, Xin Niu<sup>2</sup>, Tim R. Cressey<sup>3</sup>, Mehmet Toner<sup>1</sup>, Rebecca Sandlin<sup>1</sup>, Paul K. Drain<sup>2</sup>

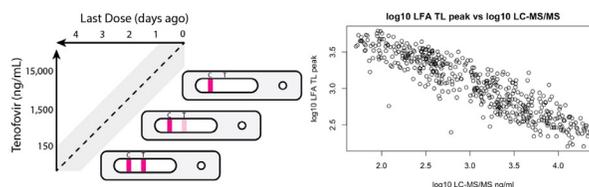
<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>Chiang Mai University, Chiang Mai, Thailand

**Background:** Objective measurements of antiretroviral adherence may be clinically useful for promoting interventions to improve prevention or treatment outcomes. In people receiving oral antiretrovirals containing tenofovir (TFV), recent adherence is correlated with the concentration of TFV in the urine. The purpose of this study was to validate our newly developed semi-quantitative LFA for urine TFV and compare its performance against LC-MS, ELISA and a commercial LFA reader.

**Methods:** We developed a semi-quantitative competitive lateral flow immunoassay (LFA) for TFV in urine, which classifies TFV levels as one of the three categories 'adequate/low/undetectable' by either optical scanner or visual scorecard. These three categories are indicated as TFV either above 1,500 ng/mL, between 150 ng/mL to 1,500 ng/mL, or below 150 ng/mL, and approximately correspond with the last oral dose having been taken 0 to 2, 2 to 4, or >4 days ago, respectively. We assessed the test using urine samples collected in a previous study of TFV pharmacokinetics following directly-observed tenofovir disoproxil fumarate. Samples were tested by LFA and liquid chromatography-mass spectrometry (LC-MS), as well as an enzyme-linked immunosorbent assay (ELISA) which we also developed. Test line intensities were scored visually 0 to 5 and quantitatively by optical LFA reader.

**Results:** 588 urine samples from 28 participants were measured, with TFV concentration ranging from <50 ng/mL to >23,200 ng/mL. LFA test line intensity was inversely proportional to TFV concentration, with a Spearman's correlation coefficient of -0.91. Visual grading performed independently by two trained personnel were concordant within 1 grade for 96% of samples. The LFA sensitivity & specificity for classifying the 1,500 ng/mL threshold by LC-MS were 87% & 92%, respectively, for the average visual reads, and 95% & 96% when read by the reader. For the 150 ng/mL 'undetectable' threshold by LC-MS, the sensitivity and specificity were 84% & 89% (visual) and 87% & 95% (reader). For the ELISA, the sensitivities & specificities for the 1,500 ng/mL and 150 ng/mL thresholds by LC-MS were 92% & 90% and 90% & 93%, respectively.

**Conclusion:** Our rapid LFA test was sensitive and specific at classifying TFV concentrations into three clinically relevant ranges. These results support the feasibility of our rapid semi-quantitative urine test using either visual score or optical readout to assess recent ingestion of TFV for treatment or prevention.



|                      | 1,500 ng/mL TFV Threshold |                 |                 |
|----------------------|---------------------------|-----------------|-----------------|
|                      | LFA - Visual              | LFA - Reader    | ELISA           |
| Sensitivity (95% CI) | 87% (83% - 91%)           | 85% (81% - 89%) | 92% (89% - 95%) |
| Specificity (95% CI) | 92% (88% - 95%)           | 96% (92% - 98%) | 90% (86% - 93%) |
|                      | 150 ng/mL TFV Threshold   |                 |                 |
|                      | LFA - Visual              | LFA - Reader    | ELISA           |
| Sensitivity (95% CI) | 84% (77% - 90%)           | 87% (81% - 92%) | 90% (83% - 94%) |
| Specificity (95% CI) | 89% (85% - 91%)           | 95% (92% - 97%) | 83% (79% - 86%) |

### 353 IMPLICATION OF MEASURING URINE TENOFOVIR BY RAPID LATERAL FLOW ASSAY FOR DOSE REGENCY

Xin Niu<sup>1</sup>, Derin Sevenler<sup>2</sup>, Sandy Dossantos<sup>2</sup>, Rebecca Sandlin<sup>2</sup>, Mehmet Toner<sup>2</sup>, Tim R. Cressey<sup>3</sup>, Paul K. Drain<sup>4</sup>

<sup>1</sup>Department of Epidemiology, University of Washington, Seattle, WA, USA, <sup>2</sup>Center for Engineering in Medicine and Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, <sup>3</sup>PHPT/IRD UMI 174, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand, <sup>4</sup>Department of Global Health, Medicine and Epidemiology, University of Washington, Seattle, WA, USA

**Background:** Using a rapid urine tenofovir (TFV) test may improve adherence counseling for PrEP/ART, but traditional lateral flow assays (LFAs) provide only limited qualitative results. We developed a new urine TFV LFA that produces both semi- and fully-quantitative results. The study aim was to characterize the quantitative LFA results of urine TFV and their relationship with time since last dosing using samples from a controlled pharmacokinetic trial.

**Methods:** We conducted a three-arm, randomized study among HIV-negative adults receiving 300 mg tenofovir disoproxil fumarate (TDF) and 200 mg emtricitabine (FTC) over a six-week directly-observed therapy (DOT) phase and four-week washout phase. Urine samples from known timepoints since last drug ingestion were tested using the rapid LFA assay. Using the same color intensity reference card, on a scale of 0-5, independent visual assessment from two lab technicians were averaged as one semi-quantitative result. LFA strips were also read within 10 minutes of test completion using an optical reader that gave fully-quantitative readings. We calculated the Spearman coefficients between LFA results and time since last dosing. We also evaluated the performance of using different cutoffs of LFA results to correctly categorize samples with different time since last dosing.

**Results:** Twenty-eight adults with 268 spot urine samples were included in this analysis. The presence of TFV resulted in no or light color signal on the LFA strip, and thus lower values of LFA results. Both semi- (averaged visual scores) and fully- (optical reader readings) quantitative LFA results increased with longer time since last dosing. The correlation coefficients between time since last dosing and averaged visual scores and optical reader readings were 0.80, and 0.83, respectively. An averaged visual score above 1.5 or an optical reading over 1500 had correctly identified all samples if their last dose was ingested more than 24 hours ago. No samples with an averaged visual score above 2.5 or an optical reading over 3000 were from participants who took their last dose within the past 48 hours.

**Conclusion:** Both averaged visual scores and optical reader readings were highly correlated with time since last dosing. Benchmarks from this study will help guide and promote future adoption of LFA as a low-cost and easy-to-perform point-of-care (POC) test for PrEP/ART adherence monitoring and interventions.

**Table 1:** Proportions of Having a Time Since Last Dose Beyond Different Time Intervals Based on Different LFA Averaged Visual Scores and Optical Reader Readings Cutoffs.

| Proportions of samples having a time since last dose beyond different time intervals based on Average Visual Scores |       |       |        |        |        |        |        |        |
|---|-------|-------|--------|--------|--------|--------|--------|--------|
| Hours since last dose   | >0.5  | >1.0  | >1.5   | >2.0   | >2.5   | >3.0   | >3.5   | >4.0   |
| >24   | 93.4% | 98.4% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| >48   | 75.8% | 86.3% | 91.9%  | 97.4%  | 100.0% | 100.0% | 100.0% | 100.0% |
| >72   | 60.8% | 72.1% | 82.6%  | 89.5%  | 98.3%  | 100.0% | 100.0% | 100.0% |
| >96   | 39.2% | 48.1% | 57.7%  | 66.7%  | 82.8%  | 96.9%  | 100.0% | 100.0% |
| >120  | 26.9% | 33.3% | 40.3%  | 47.4%  | 67.2%  | 84.4%  | 87.5%  | 66.7%  |
| >144  | 18.1% | 22.4% | 26.8%  | 31.6%  | 44.8%  | 62.5%  | 75.0%  | 33.3%  |
| >168  | 7.0%  | 8.7%  | 10.1%  | 13.2%  | 19.0%  | 34.4%  | 62.5%  | 33.3%  |

| Proportions of samples having a time since last dose beyond different time intervals based on Optical Reader Readings |       |       |       |        |        |        |        |        |
|---|-------|-------|-------|--------|--------|--------|--------|--------|
| Hours since last dose   | >500  | >700  | >1000 | >1500  | >2000  | >3000  | >4000  | >5000  |
| >24   | 94.7% | 99.0% | 99.4% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| >48   | 74.6% | 83.4% | 88.8% | 94.9%  | 99.1%  | 100.0% | 100.0% | 100.0% |
| >72   | 60.1% | 67.8% | 76.3% | 85.3%  | 94.4%  | 96.4%  | 100.0% | 100.0% |
| >96   | 38.6% | 43.2% | 50.9% | 62.5%  | 72.0%  | 87.5%  | 100.0% | 100.0% |
| >120  | 26.8% | 30.2% | 35.5% | 44.1%  | 50.5%  | 71.4%  | 91.3%  | 88.9%  |
| >144  | 18.0% | 20.1% | 23.7% | 29.4%  | 33.6%  | 50.0%  | 73.9%  | 77.8%  |
| >168  | 7.0%  | 7.5%  | 8.9%  | 11.0%  | 13.1%  | 21.4%  | 43.5%  | 66.7%  |

**Table 1:** Probability of urine TFV being below different cut-offs based on hours since last directly-observed dose in TAF-DBS

| Probability below cut-off: |           |           |           |           |           |            |                          |
|----------------------------|-----------|-----------|-----------|-----------|-----------|------------|--------------------------|
| Hours since dose           | 100 ng/ml | 200 ng/ml | 300 ng/ml | 400 ng/ml | 500 ng/ml | 1000 ng/ml | 1500 ng/ml (TDF cut-off) |
| 12                         | 0%        | 0%        | 1%        | 1%        | 3%        | 0%         | 0%                       |
| 24                         | 0%        | 0%        | 2%        | 4%        | 8%        | 29%        | 49%                      |
| 36                         | 0%        | 2%        | 7%        | 11%       | 17%       | 47%        | 67%                      |
| 48                         | 1%        | 5%        | 15%       | 22%       | 32%       | 66%        | 82%                      |
| 60                         | 2%        | 12%       | 29%       | 39%       | 50%       | 81%        | 92%                      |
| 72                         | 6%        | 25%       | 47%       | 58%       | 69%       | 91%        | 97%                      |
| 84                         | 14%       | 42%       | 66%       | 75%       | 83%       | 97%        | 99%                      |
| 96                         | 27%       | 61%       | 81%       | 88%       | 93%       | 99%        | 100%                     |
| 108                        | 45%       | 77%       | 91%       | 95%       | 97%       | 100%       | 100%                     |
| 120                        | 63%       | 89%       | 97%       | 98%       | 99%       | 100%       | 100%                     |

**354 ESTABLISHING THE CUT-OFF FOR A URINE-BASED POINT-OF-CARE TEST FOR ADHERENCE TO TAF**

**Matthew Spinelli**<sup>1</sup>, Dave Glidden<sup>1</sup>, Mary Morrow<sup>2</sup>, Samantha MaWhinney<sup>2</sup>, Kelly A. Johnson<sup>3</sup>, Hideaki Okochi<sup>1</sup>, Warren Rodrigues<sup>3</sup>, Guohong Wang<sup>3</sup>, Monica Gandhi<sup>1</sup>, Peter Anderson<sup>2</sup>

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>3</sup>Abbott Labs, Abbott Park, IL, USA

**Background:** Urine drug-level monitoring can be used to measure adherence objectively to ART or PrEP in real time. Both tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are metabolized to tenofovir (TFV). We previously developed an antibody-based immunoassay for tenofovir (TFV), and developed a point-of-care (POC) test to accurately exclude dosing in the last five days for TDF using a TFV cut-off in urine of 1500 ng/ml. Since plasma and urine levels of TFV are lower with TAF than TDF, a separate cut-off will be needed to assess TAF-based adherence. We modelled an optimal cut-off for urine TFV with TAF by using urine samples from a previously completed directly-observed therapy (DOT) study, TAF-DBS.

**Methods:** TAF-DBS randomized volunteers to 33%, 67%, or 100% adherence to TAF/emtricitabine and collected urine after 4 and 8 weeks of continuous dosing. Urine TFV levels were measured using liquid chromatography tandem mass spectrometry. An interval mixed-effects linear regression model evaluated possible cut-offs for a POC assay. The probabilities of being below a given cut-off at any time since the last dose were calculated from the model using the estimated mean, and individual and residual variation. The cut-off was optimized based on participant feedback that the assay should have high specificity for daily dosing.

**Results:** Thirty-six participants provided two urine samples each for this analysis (17 female, 7 Black, 6 Latinx). The estimated mean urine TFV concentration (ng/ml) at 24, 48, and 72 hours was 1530 (95% CI 1367-1712), 724 (95% CI: 608-861), and 342 (95% CI: 249-469) respectively. Dosing patterns were not associated with urine levels in models incorporating time since dosing (p=0.52). A tenofovir cut-off of 300 ng/ml optimized specificity for daily TAF dosing (98% probability; 95% CI: 96-100%), while maintaining high sensitivity to exclude dosing within 5 days (97% probability; 95% CI: 85-100%; Table 1).

**Conclusion:** A tenofovir cut-off of 300 ng/ml for a POC urine assay would accurately classify those with daily TAF dosing and exclude dosing within 5 days with high specificity. The interpretation of a negative test is clear: a participant would require urgent adherence counseling to avoid loss of virologic control on ART or decrease the risk of HIV acquisition on PrEP. Development of a forthcoming urine-based POC test with this cut-off will permit real-time monitoring and immediate, targeted adherence interventions for those on either TAF-based ART or PrEP.

**355 URINE TENOFOVIR CONCENTRATIONS ARE LOWER AMONG INDIVIDUALS TAKING TAF THAN TDF**

**Kelly A. Johnson**<sup>1</sup>, Matthew Spinelli<sup>1</sup>, Xin Niu<sup>2</sup>, Dave Glidden<sup>1</sup>, Samantha MaWhinney<sup>2</sup>, Mary Morrow<sup>3</sup>, Hideaki Okochi<sup>1</sup>, Tim R. Cressey<sup>4</sup>, Paul K. Drain<sup>2</sup>, Monica Gandhi<sup>1</sup>, Peter Anderson<sup>5</sup>

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>Colorado School of Public Health, Aurora, CO, USA, <sup>4</sup>Chiang Mai University, Chiang Mai, Thailand, <sup>5</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA

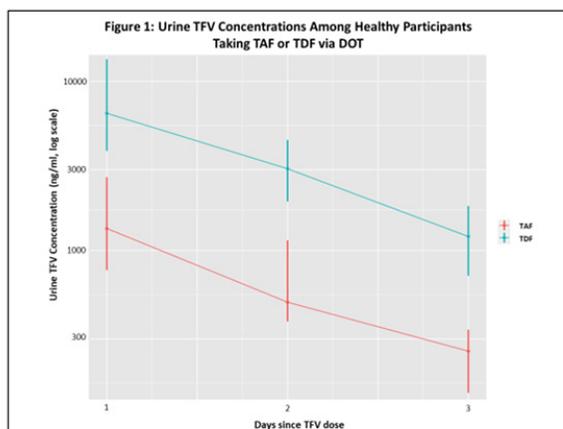
**Background:** A urine-based point-of-care (POC) immunoassay to measure urine tenofovir (TFV) levels for patients on tenofovir disoproxil fumarate (TDF) as an objective adherence metric has been developed. However, tenofovir alafenamide (TAF) is commonly used in HIV treatment and has been approved for pre-exposure prophylaxis (PrEP) among men who have sex with men. Since plasma TFV levels are nearly 10-fold lower with TAF than TDF in directly observed therapy (DOT) studies, we hypothesized that urine TFV levels would also be lower, with impacts for the POC assay. The purpose of this study was to leverage a TAF DOT study to: (1) determine urine TFV levels among individuals taking TAF at variable dosing intervals, and (2) compare them to a prior study of DOT TDF.

**Methods:** The TAF DBS-DOT study randomized healthy HIV negative adult participants to take TAF 25mg/FTC 200 mg under DOT conditions at either 33, 67, or 100% of daily dosing levels for 12 weeks. Urine specimens were collected at 4 and 8 weeks. Urine TFV levels were quantified by liquid chromatography/tandem mass spectrometry (LC/MS/MS) for participants receiving each TAF dosing strategy. Urine levels were compared to those from individuals on TDF from the previously reported TARGET DOT study. In both TARGET and a prior analysis using TAF, time since dosing, rather than dosing pattern, determined TFV urine concentration; we thus present urine concentrations as time since last dose, combined across all adherence patterns.

**Results:** TAF-DBS included 36 participants (17 female, 7 Black, and 6 Latinx), each of whom provided two urine samples, with a median age of 29 (range 18-41) and a median estimated GFR of 98 ml/min (range 78-137). The median (IQR) urine TFV levels at 24, 48, and 72 hours after last TAF dosing were 1350 (766-2710), 497 (364-1160), and 254 (144-340) ng/ml, respectively, as compared to 6480 (3885-13550), 3045 (1948-4502), and 1210 (709-1832), respectively, with TDF in the TARGET study (Figure 1).

**Conclusion:** At each assigned dosing interval, urine TFV levels on TAF were approximately 80% lower than those from participants on TDF under DOT conditions, mirroring what has been observed in plasma with DOT. Given these results, a separate, lower TFV cut-off will be needed for any POC urine assay

designed to assess TAF-based adherence on either ART or PrEP. Although the cut-off will be lower for TAF than TDF in a POC adherence assay, the cut-off is still within range to develop a lateral flow assay and such efforts are underway.



Abbreviations: TFV = Tenofovir; TAF = Tenofovir alafenamide; TDF = Tenofovir disoproxil fumarate; DOT = Directly observed therapy. Values represent median and interquartile range.

### 356 HAIR MASS SPECTROMETRY IMAGING CAPTURES SHORT- AND LONG-TERM PrEP ADHERENCE CHANGES

Joseph Mwangi<sup>1</sup>, Nicole White<sup>1</sup>, Kelly Knudtson<sup>1</sup>, Amanda Polisenio<sup>1</sup>, Craig Sykes<sup>1</sup>, Lisa Hightow-Weidman<sup>1</sup>, Angela D. Kashuba<sup>1</sup>, Elias Rosen<sup>1</sup>  
<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** Most adherence measures for antiretroviral (ARV) therapy require a blood sample, and none capture longitudinal daily adherence. We recently developed a noninvasive method for measuring daily adherence to emtricitabine (FTC)-based regimens in hair strands using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) mass spectrometry imaging (MSI), benchmarked by a directly observed therapy study. We also demonstrate daily FTC hair adherence classification for young men who have sex with men (YMSM) enrolled in the P3 (Prepared, Protected, emPowered) study who are engaged in, or initiating, preexposure prophylaxis (PrEP).

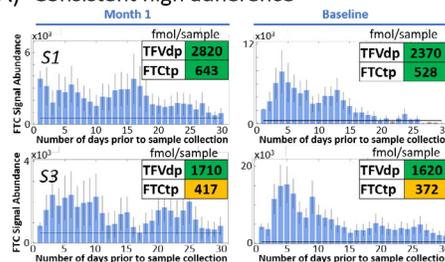
**Methods:** P3 volunteers (n=8, S1-8) reporting a range of recent adherence to PrEP at enrollment provided hair and blood samples at study initiation (T0) and after one month (T1). IR-MALDESI MSI measured FTC in the proximal 1cm (~30 days of growth) of hair strands (n=5) in 100 μm increments. Daily adherence was classified in composite longitudinal profiles. Analysis of FTC triphosphate (FTCtp) and tenofovir diphosphate (TFVdp) in dried blood spots was performed by a validated LC-MS/MS assay. IR-MALDESI and LC-MS/MS measures were compared by Spearman rank correlation (rs).

**Results:** IR-MALDESI analysis of P3 hair strands measured distinct patterns of FTC adherence at T0 and T1, which were categorized into four groups: consistently high adherence (Fig A); high adherence with occasional missed doses (Fig B); improved adherence after study initiation (Fig C); and, intermittent adherence (Fig D). Strong correlation in cumulative adherence was found between T1 TFVdp (inset) and a 60-day FTC average of concatenated T0 and T1 FTC profiles (rs=0.79, P=0.03). Agreement of recent adherence between FTCtp and the proximal 5-7 days of FTC adherence classification was variable since collecting hair by cutting close to the scalp doesn't include the most recent days of growth. In each case, the combined 30-day adherence profiling of FTC in samples collected at T0 and T1 provided a granularity of day-to-day behavior not offered by the information derived from FTCtp/TFVdp concentrations.

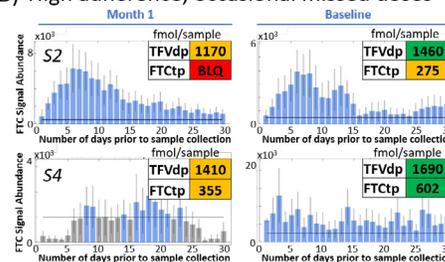
**Conclusion:** Identifying patterns of long-term dosing behavior has important implications for the care of individuals using ARVs for treatment and prevention. IR-MALDESI MSI provides a daily assessment of PrEP adherence in hair, reflecting both short-term and long-term behavior.

### Profiles of Longitudinal Daily PrEP Adherence by IR-MALDESI

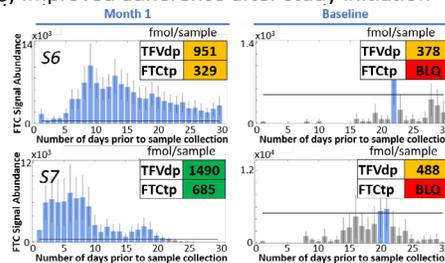
#### A) Consistent high adherence



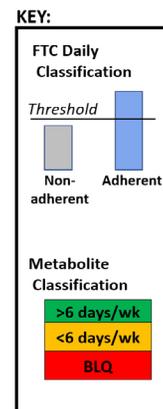
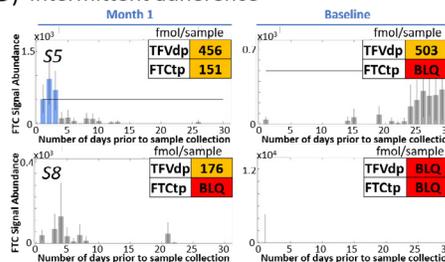
#### B) High adherence, occasional missed doses



#### C) Improved adherence after study initiation



#### D) Intermittent adherence



### 357 HAIR MASS SPECTROMETRY IMAGING OF DAILY MARAVIROC ADHERENCE IN HPTN 069/ACTG 5305

Elias Rosen<sup>1</sup>, Nicole White<sup>1</sup>, Mac Gilliland<sup>2</sup>, Monica Gandhi<sup>3</sup>, Roy M. Gulick<sup>4</sup>, Angela D. Kashuba<sup>1</sup>

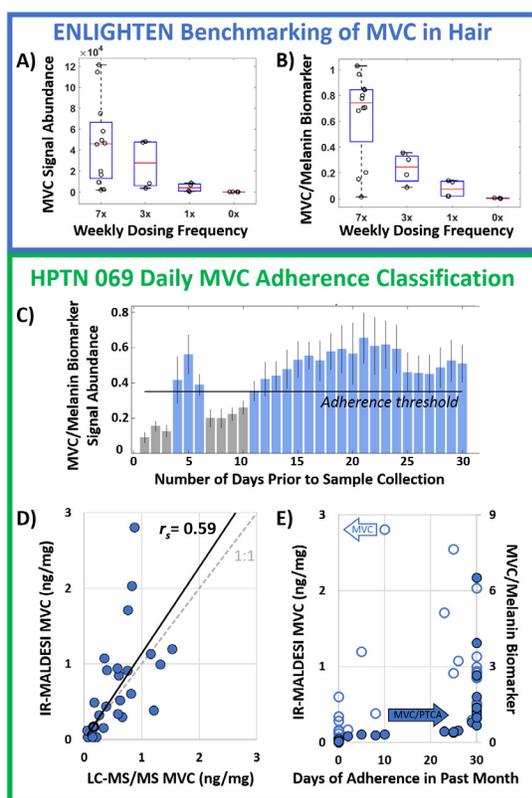
<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>Furman University, Greenville, SC, USA, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA, <sup>4</sup>Weill Cornell Medicine, New York, NY, USA

**Background:** Drug concentrations in hair can provide long-term measures of adherence. Classifying adherence by drug concentration may be less accurate for melanin-bound compounds like maraviroc (MVC) since darker hair colors can absorb greater amounts of drug. Using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) mass spectrometry imaging (MSI) in the ENLIGHTEN study, we benchmarked longitudinal MVC profiles in hair following directly observed therapy (DOT) of daily and intermittent dosing. We scaled these measures with a melanin biomarker (pyrrole tricarboxylic acid, PTCA) to improve MVC adherence benchmarks. These criteria were applied in HPTN 069/ACTG 5305 (069/5305) to assess daily adherence to MVC-based PrEP regimens. **Methods:** IR-MALDESI MSI measured MVC in the proximal 1-2cm and PTCA in the distal 0.5cm of the same 4 hair strands. Quantification of MVC in hair was

based on a calibration curve from incubated hair strands (LLOQ: 0.12 ng/mg hair). Benchmarking was performed in samples from 12 volunteers undertaking 28-day phases of daily and then intermittent (0x, 1x, or 3x/wk; n=4 in each group) MVC dosing in the ENLIGHTEN study. MVC dose-frequency benchmarks were identified in longitudinal profiles and normalized by PTCA, with an adherence threshold determined by an ROC curve. For 069/5305, MVC was measured by LC-MS/MS and IR-MALDESI in 32 samples from 19 individuals over matched segment lengths of 1cm (~1 month of growth).

**Results:** Overlapping MVC dose-frequency ranges in ENLIGHTEN DOT samples (Fig. A) were resolved by PTCA normalization (Fig. B) [MVC/PTCA: daily median (interquartile range) 0.75 (0.44–0.85); 3x/wk 0.25 (0.14–0.33); 1x/wk 0.08 (0.02–0.14); 0x/wk 0.0 (0.0–0.01)]. A threshold of MVC/PTCA=0.35 was selected to classify daily adherence with 75% sensitivity and 100% specificity. Month-long adherence patterns were evaluated for 069/5305 samples (Fig. C). Strong correlation was found between IR-MALDESI and LC-MS/MS MVC concentrations (Fig. D; Spearman's rho=0.59, P=0.007). MVC/PTCA yielded unambiguous adherence classification relative to MVC alone (Fig. E), indicating only 8/19 individuals adhered to a daily regimen throughout the prior month.

**Conclusion:** Hair color is an important factor for accurate adherence classification of MVC, and likely other antiretrovirals with similar physicochemical properties. Long-term, daily adherence classification of PTCA-scaled MVC was demonstrated by IR-MALDESI MSI and found less than expected 069/5305 adherence.



### 358 TOTAL AND UNBOUND DORAVIRINE CONCENTRATIONS AND VIRAL SUPPRESSION IN CSF OF HIV+ PTS

Juan M. Tiraboschi<sup>1</sup>, Sofia Scevola<sup>1</sup>, Sujian D. Penchala<sup>2</sup>, Laura Else<sup>2</sup>, Paula Prieto<sup>1</sup>, Maria Saumoy<sup>1</sup>, Jordi Niubo<sup>1</sup>, Benito Garcia-Vidal<sup>1</sup>, Saye Khoo<sup>2</sup>, Daniel Podzamczar<sup>1</sup>

<sup>1</sup>Bellvitge University Hospital, Barcelona, Spain, <sup>2</sup>University of Liverpool, Liverpool, UK

**Background:** Doravirine (DOR) is a new HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) that has demonstrated a good efficacy and safety profile in clinical trials. Initial pharmacokinetic studies demonstrated a time to maximal concentration of 1–5 h, not extensive binding to plasma proteins (76%) and poor solubility in water. In animal models the tissue distribution was assessed using 14C-labelled DOR. Low levels of radioactivity were observed in the brain suggesting that DOR does not readily cross the

blood-brain-barrier. We determined DOR levels in cerebrospinal fluid (CSF) as well as HIV viral load in this compartment in HIV-1 virologically suppressed patients.

**Methods:** This is a single-arm, open-label, single-center study. After an initial assessment, 15 participants switched from stable ART to Emtricitabine/Tenofovir alafenamide (FTC/TAF) plus DOR 100 mg OD orally. At week 4, blood and CSF samples were collected 24 h post dose, when DOR concentrations are expected to be lowest. Total DOR concentrations in plasma and CSF were determined using a validated LC-MS method. Unbound DOR concentrations were determined using Rapid Equilibrium Dialysis. HIV RNA was measured in plasma and CSF by RT-PCR (LLQ 20 copies/mL).

**Results:** A total of 14 plasma and 15 CSF samples were collected. Median age was 47 years (27–65), 86% were male. At baseline, median CD4 cell count and HIV viral load in plasma were 773 cells/uL (372 – 1744) and <20 copies/ml respectively. Most patients switched from INSTI based regimens [Bictegravir (5); Dolutegravir (4) and Elvitegravir (3)]. At week 4, only one patient had detectable viral load in CSF (32 copies/ml) while undetectable in blood plasma. The DOR unbound fraction in plasma and CSF were 12.8% and 76.1% respectively. DOR total CSF/total plasma ratio was 0.13. DOR total CSF/unbound plasma was 0.99, suggesting that DOR crosses the blood brain barrier primarily via passive diffusion (Table 1).

**Conclusion:** Total and unbound trough DORA concentrations in CSF exceeded the EC<sub>50</sub> value against WT virus (5.1 ng/mL) by 11.4 and 8.7-fold respectively, suggesting that DOR in combination with FTC/TAF may contribute to inhibit viral replication in this compartment.

Table 1. Individual plasma and CSF data after 4 weeks with DOR+ FTC/TAF.

| ID      | HIV RNA plasma copies/ml | HIV RNA CSF copies/ml | Total plasma DOR ng/ml | Unbound plasma DOR ng/ml | Total CSF DOR ng/ml | Unbound CSF DOR ng/ml | totalCSF/totalplasma | totalCSF/unboundplasma |
|---------|--------------------------|-----------------------|------------------------|--------------------------|---------------------|-----------------------|----------------------|------------------------|
| 1       | <20                      | <20                   | 385.9                  | 37.8                     | 38.7                | 24.7                  | 0.10                 | 1.02                   |
| 2       | <20                      | <20                   | 942.2                  | 104.7                    | 127.3               | 105.0                 | 0.11                 | 1.22                   |
| 3       | <20                      | <20                   | 281.7                  | 36.0                     | 37.2                | 25.8                  | 0.13                 | 1.03                   |
| 4       | <20                      | N/D                   | 535.7                  | 89.2                     | 66.2                | 50.8                  | 0.17                 | 0.74                   |
| 5       | <20                      | 32                    | 546.4                  | 61.2                     | 79.4                | 60.3                  | 0.11                 | 1.30                   |
| 6       | <20                      | <20                   | 912.9                  | 115.5                    | 102.8               | 80.6                  | 0.13                 | 0.89                   |
| 7       | <20                      | <20                   | 447.1                  | 60.5                     | 40.9                | 29.0                  | 0.14                 | 0.68                   |
| 8       | <20                      | <20                   | 313.9                  | 39.7                     | 38.0                | 26.8                  | 0.13                 | 0.96                   |
| 9       | <20                      | <20                   | 527.8                  | 71.5                     | 58.6                | 44.6                  | 0.14                 | 0.82                   |
| 10      | 76                       | <20                   | 169.5                  | 21.3                     | 26.1                | 17.9                  | 0.13                 | 1.22                   |
| 11      | <20                      | <20                   | 535.1                  | 58.0                     | 59.1                | 48.7                  | 0.11                 | 1.02                   |
| 12      | <20                      | <20                   | 181.6                  | 24.7                     | 23.2                | 14.9                  | 0.14                 | 0.94                   |
| 13      | <20                      | <20                   | 230.3                  | 36.7                     | 28.8                | 17.8                  | 0.16                 | 0.78                   |
| 14      | <20                      | <20                   |                        |                          | 85.5                | 72.1                  | N/D                  | N/D                    |
| 15      | <20                      | <20                   | 388.1                  | 49.0                     | 75.0                | 64.6                  | 0.13                 | 1.53                   |
| Median  |                          |                       | 417.6                  | 53.5                     | 58.6                | 44.6                  | 0.13                 | 0.99                   |
| (range) |                          |                       | (169.5-942.2)          | (21.3-115.5)             | (23.2-127.3)        | (14.9-105.0)          | (0.09-0.19)          | (0.68-1.53)            |

### 359 PERSISTENT HIV TRANSCRIPTION AND VARIABLE ARV LEVELS IN LYMPH NODES DURING ART

Courtney V. Fletcher<sup>1</sup>, Eugene Kroon<sup>2</sup>, Timothy Schacker<sup>3</sup>, Suteeraporn Pinyakorn<sup>4</sup>, Nicolas Chomont<sup>5</sup>, Suthat Chottanapund<sup>2</sup>, Peeriya Prueksakaw<sup>2</sup>, Khunthalee Benjapornpong<sup>2</sup>, Supranee Buranapraditkun<sup>6</sup>, Jintanat Ananworanich<sup>7</sup>, Sandhya Vasani<sup>4</sup>, Denise C. Hsu<sup>4</sup>, for the RV254/SEARCH 010 Study Group

<sup>1</sup>University of Nebraska Medical Center, Omaha, NE, USA, <sup>2</sup>SEARCH, Institute of HIV Research and Innovation, Bangkok, Thailand, <sup>3</sup>University of Minnesota, Minneapolis, MN, USA, <sup>4</sup>US Military HIV Research Program, Silver Spring, MD, USA, <sup>5</sup>Centre de Recherche du CHUM, Montreal, Canada, <sup>6</sup>Chulalongkorn University, Bangkok, Thailand, <sup>7</sup>University of Amsterdam, Amsterdam, Netherlands

**Background:** The ability of antiretroviral (ARV) drugs to penetrate and suppress viral replication in tissue reservoir sites is critical for HIV remission. We evaluated ARV levels and their impact on HIV transcription in lymph nodes (LN).

**Methods:** This was a sub-study involving participants of the RV254/SEARCH010 Acute HIV Infection Cohort in Bangkok, Thailand. Group 1 (n=6) initiated and continued ARVs with 2 NRTI, dolutegravir (DTG) and maraviroc (MVC). Group 2 (n=12) initiated ARVs on 2 NRTI plus efavirenz and were switched to 2 NRTI plus DTG. HIV RNA+ and DNA+ cells were measured by RNAscope®. Cell-associated HIV RNA and total HIV DNA were measured by PCR. ARV levels were measured by liquid chromatography, tandem mass spectrometry.

**Results:** Participants, median age 27 yrs, were all MSM. At LN biopsy all had plasma HIV-RNA <20 copies/mL. Group 2 had longer durations of ARV (median 135wks, p<0.001) and DTG use (median 63wks, p=0.002) compared to group 1 (median 44wks, Table). Fiebig stage, HIV viral load, CD4 and CD8 T cell counts at baseline and at LN biopsy were not different between groups. Median PBMC levels (fmol/10<sup>6</sup> cells) were: TFV-DP, 32; 3TC-TP, 8390; CBV-TP, 45. LN cellular levels (Table) of TFV-DP, 3TC-TP, DTG and MVC were measured in all participants; CBV-TP was quantifiable in 4/14 (29%) vs 100% of PBMC samples. Median ratios of LN cellular to in-vitro inhibitory levels (IC<sub>50</sub>-or-90) were: TFV-DP, 1.8; 3TC-TP, 4.1; CBV-TP, 0.5 (in n=4 with quantifiable levels); DTG, 0.8; MVC, 38.8. Ongoing viral expression was detected by RNAscope® in all participants. There were trends for lower RNA+ (median of 71350 vs 99750 cells/g, p=0.111) and DNA+ cells (median 169137.5 vs 303389 cells/g, p=0.512) in group 1 vs 2. PBMC levels of cell-associated HIV RNA and total HIV DNA were not different between groups.

**Conclusion:** PBMC levels of TFV-DP, 3TC-TP and CBV-TP were consistent with literature values, as were LN levels of TFV-DP and 3TC-TP. This is the first report of LN penetration of CBV-TP and MVC. CBV-TP LN levels were commonly not quantifiable and <math>=^{\*\*\*} div=^{\*\*\*}>

| Characteristics  | All 1+2 (N=18)             | Group 1 (N=6)<br>(2NRTI, DTG and MVC) | Group 2 (N=12)<br>(2NRTI and DTG) | P-value |
|--|----------------------------|---------------------------------------|-----------------------------------|---------|
| ARV duration, week   | 109 (24 - 252)             | 44 (24 - 54)                          | 135 (86 - 252)                    | <0.001  |
| DTG duration, week   | 59 (24 - 82)               | 44 (24 - 54)                          | 63 (42 - 82)                      | 0.002   |
| ARV regimen  |                            |                                       |                                   | <0.001  |
| ABC/3TC/DTG/MVC  | 3 (16.7)                   | 3 (50)                                | -                                 |         |
| TDF/3TC/DTG/MVC  | 3 (16.7)                   | 3 (50)                                | -                                 |         |
| ABC/3TC/DTG  | 11 (61.1)                  | -                                     | 11 (91.7)                         |         |
| TDF/3TC/DTG  | 1 (6.6)                    | -                                     | 1 (8.3)                           |         |
| ARV levels in LN   |                            |                                       |                                   |         |
| TFV-DP (fmol/10 <sup>6</sup> cells)                        | 91.2 (66.1 - 122.7)        | 114.6 (66.1 - 122.7)                  | 67.8 (67.8 - 67.8)                | 0.655   |
| 3TC-TP (fmol/10 <sup>6</sup> cells)                        | 2314.8 (654.3 - 5575)      | 2112.5 (1563.1 - 3283.1)              | 2482.2 (654.3 - 5575)             | 0.190   |
| CBV-TP (fmol/10 <sup>6</sup> cells)                        | 16.2* (BLQ - 20.2)         | BLQ                                   | 16.2* (BLQ - 20.2)                | 0.266   |
| DTG (fmol/10 <sup>6</sup> cells)                           | 35.2 (4.6 - 120.3)         | 46.6 (35.2 - 120.3)                   | 28.3 (4.6 - 100.2)                | 0.025   |
| MVC (fmol/10 <sup>6</sup> cells)                           | 969.3 (401.1 - 1577)       | 969.3 (401.1 - 1577)                  | -                                 | NA      |
| HIV Load in LN   |                            |                                       |                                   |         |
| RNAscope (+ cells/g tissue)                                | 91400 (52600 - 276000)     | 71350 (52600 - 109000)                | 99750 (55000 - 276000)            | 0.111   |
| DNAscope (+ cells/g tissue)                                | 262319 (105145.4 - 769000) | 169137.5 (135000 - 543101)            | 303389.3 (105145.4 - 769000)      | 0.512   |
| HIV Load in PBMC   |                            |                                       |                                   |         |
| Total HIV DNA (copies/10 <sup>6</sup> cells)               | 5.5 (0 - 297.1)            | 16.4 (0.1 - 26.5)                     | 2.7 (0 - 297.1)                   | 0.851   |
| Cell-associated RNA (LTR:rag copies/10 <sup>6</sup> cells) | 0 (0 - 410.9)              | 0 (0 - 17.8)                          | 0 (0 - 410.9)                     | 0.394   |
| Ratio caRNA/Total DNA                                      | 0 (0 - 255.5)              | 0 (0 - 255.5)                         | 0 (0 - 52.1)                      | 0.910   |

Table 1: ARV levels and HIV Load at the time of lymph node biopsy  
Values are presented as median (min-max) for continuous variables or n (%) for categorical variables.  
\* median from n=4 with quantifiable concentrations

**360 PBPK MODELS OF TFV EXPOSURE IN LYMPH NODES REVEAL PERMEABILITY-LIMITED DISTRIBUTION**

Erin M. Scholz<sup>1</sup>, Yanguang Cao<sup>1</sup>, Angela D. Kashuba<sup>1</sup>

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** Despite antiretroviral (ARV) therapy, HIV persists in lymphoid tissue throughout the body. Lymph node ARV penetration is crucial for HIV treatment and eradication, but sampling these tissues is highly invasive and costly. Here, we investigate whether a novel physiologically-based pharmacokinetic (PBPK) model can predict the concentration of tenofovir (TFV) in lymph nodes of nonhuman primates (NHPs) and humans.

**Methods:** Model development followed the same stepwise approach in NHPs and humans. First, a whole-body PBPK model of TFV was developed in PK-Sim using built-in physiologic parameters, drug parameters, and plasma clearance estimates. The model was fit to observed data of TFV concentrations in plasma and tissue (brain, ileum, rectum) by optimizing interstitial-intracellular permeabilities. The final plasma model was exported from PK-Sim to MoBi, where a lymph node compartment was added. Physiologic parameters describing the lymph node were obtained from literature. The lymph node model was exported back to PK-Sim, and fit to observed data by optimizing the lymph node interstitial-intracellular permeability (PLN) and tissue:plasma partition coefficient (KpLN). Model acceptance was determined by PK parameter validation against reference values; ratios within 0.5-2 were considered predictive.

**Results:** Mean PK parameters, reference values, and ratios for the final NHP and human lymph node models are summarized in the table. Both species' models passed acceptance criteria across all PK parameters, within 0.6-1.7 fold of directly measured values. Optimized PLN increased from baseline (1.29e-6 cm/min) in both the NHP (3.74e-5 cm/min) and human models (8.66e-6 cm/min), indicating that a permeability-limited model best described TFV kinetics

in the lymph node. Optimized KpLN ≈1 in NHPs (0.95) and humans (0.81), and was similar to the partition coefficients of other organs, consistent with TFV's volume of distribution (~0.8 L/kg).

**Conclusion:** Our novel PBPK model is the first to predict TFV concentrations in lymph nodes of NHPs and humans. A permeability-limited lymph node model and KpLN ≈1 accurately captures TFV's rapid diffusion between plasma and tissue, which is expected based on its low lipophilicity, molecular weight, and minimal protein binding. Our PBPK model can be used to describe the lymph node distribution of ARVs with similar properties (FTC, 3TC), or to test new formulations aimed at increasing lymphatic penetration.

| Parameter      | NHP PBPK | NHP reference | Reference: model ratio | Human PBPK | Human reference | Reference: model ratio |
|----------------|----------|---------------|------------------------|------------|-----------------|------------------------|
| AUC (ng*hr/mL) | 53,206   | 70,100        | 1.32                   | 3,377      | 3,324           | 0.98                   |
| Cmax (ng/mL)   | 45,184   | 43,200        | 0.96                   | 253        | 326             | 1.30                   |
| Cmin (ng/mL)   | 26       | 18.5          | 0.71                   | 46         | 64.4            | 1.40                   |
| Half-life (hr) | 9.5      | 6             | 0.63                   | 10         | 17              | 1.70                   |

**361 PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF TFV AND TAF FOR PrEP IN FORESKIN TISSUE**

Carolina Herrera<sup>1</sup>, Laura Else<sup>2</sup>, Sujan D. Penchala<sup>2</sup>, Azure-Dee A. Pillay<sup>2</sup>, Thabiso B. Seiphetho<sup>3</sup>, Limakatso Lebina<sup>4</sup>, Christian Callebaut<sup>5</sup>, Neil A. Martinson<sup>4</sup>, Julie Fox<sup>6</sup>, Saye Khoo<sup>2</sup>

<sup>1</sup>Imperial College London, London, UK, <sup>2</sup>University of Liverpool, Liverpool, UK, <sup>3</sup>University of Cape Town, Cape Town, South Africa, <sup>4</sup>University of the Witwatersrand, Johannesburg, South Africa, <sup>5</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>6</sup>Guy's and St Thomas' NHS Foundation Trust-King's College London, London, UK

**Background:** Pre-exposure prophylaxis (PrEP) studies have focussed predominantly on the efficacy in female reproductive and colorectal tracts, with limited research on the efficacy of PrEP candidates in the male genital tract. We assessed the ex vivo pharmacological profile of Tenofovir (TFV) and Tenofovir alafenamide (TAF) in foreskin tissue to inform the design of the CHAPS oral PrEP trial (NCT03986970).

**Methods:** Foreskin specimens were obtained with signed informed consent from HIV-negative males who voluntarily requested medical circumcision. Inner mucosal and outer skin were cut in explants and exposed to serial dilutions of TFV or TAF for 1h prior to addition of HIV-1...BaL at a high (HVT) or a low viral titre (LVT) for 2h. Infection was assessed at different time points during 15 days of culture by measurement of p24 in culture supernatants. TFV, TAF and TFV-diphosphate (TFV-DP) concentrations were measured in tissue, culture supernatants and dosing and washing solutions using LC-MS methods.

**Results:** Dose-response curves were obtained for both drugs against the two viral titres tested with greater inhibitory potency observed against LVT. Inhibitory equivalency mimicking oral dosing was defined between 1 mg/ml of TFV and 15 µg/ml of TAF against HVT for the dosing post-ex vivo challenge included in the design of CHAPS trial. Concentrations of TFV-DP in foreskin explants were at least 5 times higher after ex vivo dosing with TAF vs. TFV. Statistically significant negative linear correlations were observed between explant TFV-DP levels and p24 concentrations following HVT (r...2=0.6867, P=0.0001 for TFV and r...2=0.6696, P=0.0002 for TAF).

**Conclusion:** Pre-clinical evaluation of TAF reveals greater potency than TFV against penile HIV transmission. Ex vivo dose-challenge studies in human foreskin explants can be used as surrogate for in vivo studies to compare doses and preventive agents to be included in clinical trials.

**362 DORAVIRINE CONCENTRATIONS AND HIV-1 RNA SUPPRESSION IN MALE AND FEMALE GENITAL FLUIDS**

Sofia Scevoli<sup>1</sup>, Arkaitz Imaz<sup>2</sup>, Mackenzie L. Cottrell<sup>2</sup>, Jordi Niubo<sup>1</sup>, Juan M. Tiraboschi<sup>1</sup>, Sandra Morenilla<sup>1</sup>, Irene Soriano<sup>1</sup>, Angela D. Kashuba<sup>3</sup>, Daniel Podzamczar<sup>1</sup>

<sup>1</sup>Bellvitge University Hospital, Barcelona, Spain, <sup>2</sup>Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, <sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** Residual HIV replication in reservoirs might contribute to immune activation and inflammation and constitutes a barrier to eradication. Antiretroviral distribution in male and female genital tract is required to suppress HIV replication within these compartments. We determined doravirine concentrations and HIV-1 RNA in blood plasma (BP), seminal plasma (SP) and

cervicovaginal fluid (CVF) of HIV-1-infected adults receiving ART with doravirine plus emtricitabine/tenofovir alafenamide (DOR+FTC/TAF).

**Methods:** This prospective study included 15 male and 15 female HIV-1 infected, virologically suppressed adults on stable ART. ART was switched to DOR+FTC/TAF. After 8 weeks, total and protein-unbound DOR concentrations were determined at the end of a dosing interval (C24h) in paired SP/CVF and BP samples. HIV-1 RNA was evaluated in SP/CVF and BP samples at baseline and week 8. Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to quantify DOR concentrations, and HIV-1 RNA was determined by real-time PCR (Abbott). Data are presented as median (range).

**Results:** 15 males and 14 females completed the study and were included in the analysis. Age was 41 years (23–62), time on ART 109 months (16–305) and CD4 count 791 cells/μL (329–1926). At baseline, all subjects had HIV-1 RNA <40 copies/mL in SP and CVF samples. Eight weeks after switching to DOR+FTC/TAF, total DOR C24h was 127 ng/mL (31.2–272) in SP and 506 ng/mL (200–961) in CVF, corresponding to 35% and 106% of total DOR concentrations in BP, respectively. DOR protein-unbound fractions were 82.2% in SP and 63.5% in CVF. Protein-unbound DOR C24h was 104 ng/mL (27–218) in SP and 312 ng/mL (138–562) in CVF (Table 1). Thus, median protein-unbound DOR C24h in SP and CVF were 20.4-fold and 61.2-fold above the half-maximal effective concentration value (EC<sub>50</sub>) for wild-type HIV-1 (5.1 ng/mL). At week 8, all individuals maintained HIV-1 RNA suppression <40 copies/mL in BP and genital fluid samples with the exception of one male with detectable HIV-1 RNA (263 copies/mL) in SP despite a high DOR concentration in this compartment (protein-unbound C24h 104 ng/mL).

**Conclusion:** Protein-unbound DOR concentrations in SP and CVF highly exceeded the EC<sub>50</sub> value for wild-type HIV-1 in all individuals. DOR+FTC/TAF seems effective to maintain HIV-1 RNA suppression in SP and CVF.

**Table 1:** Doravirine concentrations (C<sub>24h</sub>) in blood plasma, seminal plasma and cervicovaginal fluid

| Sex | Males                                     |                                  | Females                                    |                                   | CVF:BP ratio Total drug | CVF:BP ratio Protein-unbound drug |
|-----|---|----------------------------------|--|-----------------------------------|-------------------------|-----------------------------------|
|     | C <sub>24h</sub> Total Drug in BP (ng/mL) | Protein-bound fraction in BP (%) | C <sub>24h</sub> Total drug in SP (ng/mL)  | Protein-bound fraction in SP (%)  |                         |                                   |
|     | 363 (77.1–566)                            | 81.3 (58.4–86.3)                 | 127 (31.2–272)                             | 12.8 (0–23)                       | 0.35 (0.40–0.48)        | 1.53 (0.83–2.82)                  |
|     |   |                                  |  |                                   |                         |                                   |
| Sex | Males                                     |                                  | Females                                    |                                   | CVF:BP ratio Total drug | CVF:BP ratio Protein-unbound drug |
|     | C <sub>24h</sub> Total Drug in BP (ng/mL) | Protein-bound fraction in BP (%) | C <sub>24h</sub> Total drug in CVF (ng/mL) | Protein-bound fraction in CVF (%) |                         |                                   |
|     | 479 (306–818)                             | 82.7 (75.5–85.4)                 | 506 (200–961)                              | 36.6 (21–55.4)                    | 1.06 (0.65–1.17)        | 3.75 (1.85–4.71)                  |

### 363 PREDICTED SUCCESS OF PrEP USERS' PREFERRED NONDAILY TENOFOVIR/EMTRICITABINE REGIMENS

**Julie B. Dumond**<sup>1</sup>, Mackenzie L. Cottrell<sup>1</sup>, Allison E. Symonds<sup>1</sup>, Craig Sykes<sup>1</sup>, Nicole White<sup>1</sup>, Angela D. Kashuba<sup>1</sup>

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** Adherence is critical for effective HIV pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), yet remains a clinical challenge. TDF/FTC PrEP users are interested in less-than-daily and event-driven dosing [PMCID: PMC7228850]. Using a published model of TDF/FTC pharmacokinetics/pharmacodynamics (PK/PD) in rectal (RT), cervical (CT), and vaginal (VT) tissue [PMCID: PMC4907409], we predicted the efficacy of several dosing schedules being used off-label by PrEP users.

**Methods:** For each regimen, 1000 virtual PK profiles were simulated (NONMEM 7.4) for TDF and FTC; as per PMC4907409, drug metabolite: endogenous nucleotide (EN) ratios were created from simulated concentrations of tenofovir diphosphate (TFVdp) and FTC triphosphate (FTCtp) and randomly sampled EN (dATP and dCTP, for TFVdp and FTCtp, respectively) concentrations for each tissue. These ratios predicted the synergistic effect of TDF/FTC, with model parameters derived from in vitro CD4+ cell experiments. Maximal efficacy (ME) was defined as ≥95% of profiles >EC<sub>90</sub>; the % of profiles achieving this are presented. Regimens included Friday/Saturday (FS) dosing, Tuesday/Thursday/Saturday/Sunday (TTSS) dosing, and 3 pericoital regimens with the 2nd dose occurring 24, 36, or 48 hrs after the 1st dose.

**Results:** In the 1st week, FS and TTSS do not achieve ME in RT until 27hr and 40hr post-1st dose, respectively; repeated dosing predicts ME within the 1st week and ongoing RT ME. For pericoital regimens, ME in RT occurred after the 2nd dose, at 30 hr, 38 hr, and 49hr for the 24hr, 36hr and 48 hr regimens, respectively. Within 4hr of 1st dose, ~50% of RT profiles achieved ME; ~88% achieved it 24hr post-dose. No regimen achieves ME in CT; ~70% of CT profiles

achieved EC<sub>90</sub> at 24hr post-dose. ME was achieved in VT within 4hr of 1st dose, but 50% of profiles were <=

**Conclusion:** With this approach, we predict pericoital dosing of an initial single-dose of TDF/FTC will be 82% protective in MSM and 70% protective in women.

An initial double-dose, such as in IPERGAY, is needed for the best chance of immediate ME in men and women [PMC7228850], though women are protected for less time post-coitus. Consistent with earlier work showing CT/VT requires ≥4 doses/week but RT requires ≥2 doses/week to achieve ME, regular FS dosing is a viable PrEP strategy for anal intercourse but is unlikely to be protective for vaginal intercourse.

| Regimen   | Trough Time                            | % Achieving EC <sub>90</sub> in RT | % Achieving EC <sub>90</sub> in CT | % Achieving EC <sub>90</sub> in VT |
|---|--|------------------------------------|------------------------------------|------------------------------------|
| 0 hr, 24 hr pericoital FS dosing  | 23.5 hr (first dose)                   | 88.2                               | 78.9                               | 99.4                               |
| 0 hr, 36 hr pericoital  | 35.5 hr (first dose)                   | 92.3                               | 69.3                               | 95.8                               |
| 0 hr, 48 hr pericoital, TTSS dosing   | 47.5 hr (first dose)                   | 94.5                               | 58.4                               | 83.6                               |
| 2x/week dosing*   | 83.5 hr (steady-state)                 | 99                                 | 65                                 |                                    |
| 4x/week dosing*   | 41.5 hr (steady-state)                 | 99                                 | 95                                 |                                    |
| 7x/week dosing*   | 23.5hr (steady state)                  | 100                                | 100                                |                                    |
| IPERGAY (double dose 2-24 hr pre-coitus, followed by single dose every 24 hours post-coitus x 2)* | Coitus (2hr, 24hr after a double dose) | 81 (2hr)<br>98 (24 hr)             | 98 (2hr)<br>100 (24 hr)            |                                    |

\*As reported in PMC4907409; female genital tract concentrations were reported as the composite of CT and VT as "lower female genital tract tissue".

364



### HIGH LUNG LEVELS OF ACTIVE TRIPHOSPHATE PREDICTED WITH ORAL AT-527 IN COVID PATIENTS

**Xiao-Jian Zhou**<sup>1</sup>, Arantxa Horga<sup>1</sup>, Gaetano Morelli<sup>2</sup>, Maureen Montron<sup>1</sup>, Keith Pietropaolo<sup>1</sup>, Bruce Belanger<sup>1</sup>, Steven S. Good<sup>1</sup>, Adel Moussa<sup>1</sup>, Janet Hammond<sup>1</sup>, Jean-Pierre Sommadossi<sup>1</sup>

<sup>1</sup>Atea Pharmaceuticals, Inc, Boston, MA, USA, <sup>2</sup>Altasciences, Montreal, Canada

**Background:** AT-527 is a guanosine nucleotide prodrug with potent in vitro antiviral activity against flaviviruses and coronaviruses including SARS-CoV-2 (EC<sub>50</sub>=0.5 μM), the virus responsible for COVID-19. AT-527 exhibits a unique mechanism of action predominantly targeting the NiRAN function of the SARS-CoV-2 polymerase. The clinical safety to date and in vitro potency of AT-527 prompted evaluation of this drug candidate in patients with COVID-19. The purpose of this study was to assess the safety and pharmacokinetics (PK) of AT-527 dosed 550 mg twice a day (BID) in healthy subjects and to predict human lung exposure of the active triphosphate metabolite AT-9010.

**Methods:** Twenty healthy subjects were randomized 1:1 to receive orally AT-527 550 mg BID or matching placebo for 5 days. Safety assessments included adverse events (AEs), vital signs, electrocardiograms (ECGs) and standard safety laboratory tests. Intensive PK sampling was performed after the first and last two doses and assayed for plasma AT-511, the free base form, and metabolites including AT-273, the guanosine nucleoside metabolite, a surrogate for intracellular AT-9010.

**Results:** AT-527 was well tolerated with no discontinuations, serious AEs, clinically significant changes in vital signs or ECGs based on still blinded safety data. AT-511 was rapidly absorbed followed by fast and extensive metabolic conversion to an L-alanyl intermediate metabolite AT-551 and ultimately intracellular AT-9010, reflected by plasma AT-273. Steady state levels were quickly achieved by the third dose of AT-527. Plasma levels of AT-273 were used to predict lung concentrations of AT-9010 using a scaling factor of 1.2X previously determined from in vivo tissue distribution of the triphosphate metabolite in cynomolgus monkeys. As early as 3 hours after the first dose and maintained from the second dose throughout 5 days of dosing, the predicted lung AT-9010 levels were consistently above the EC<sub>50</sub> of the drug candidate in inhibiting SARS-CoV-2 replication in vitro.

**Conclusion:** AT-527 orally administered with a regimen of 550 mg BID for 5 days was well-tolerated in healthy subjects. A favorable PK profile was demonstrated: rapid attainment of steady state with a fast build-up of trough levels of AT-273, which were reflective of efficacious active triphosphate metabolite levels in the lungs. AT-527, with a 550 mg BID dosing regimen, is

currently being evaluated in Phase 2 clinical studies as an early treatment option for COVID-19.

### 365 INTEGRATED DMPK ALGORITHM FOR THE PREDICTION OF ARV DDI MAGNITUDE

**Sandra Grañana-Castillo**<sup>1</sup>, Fazila S. Bunglawala<sup>1</sup>, Nicolas Cottura<sup>1</sup>, Asangaedem Akpan<sup>1</sup>, Rachel Bearon<sup>1</sup>, Saye Khoo<sup>1</sup>, Marco Siccardi<sup>1</sup>

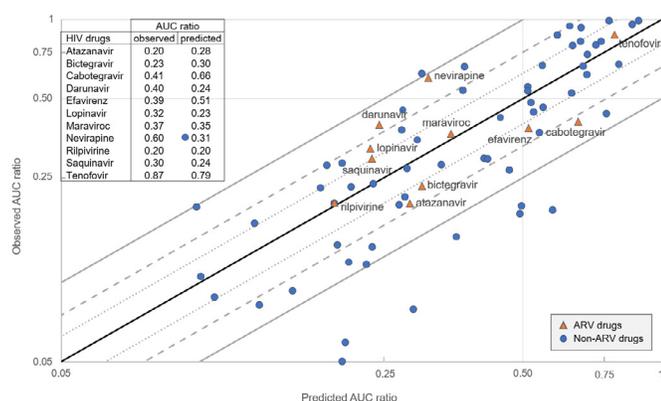
<sup>1</sup>University of Liverpool, Liverpool, UK

**Background:** The prevalence of potential drug-drug interactions (DDIs) is about 29% in people living with HIV (PLWH) undergoing treatment, which can impact the overall management of therapies. Only a minority of potential DDIs have actually been characterised in clinical studies; many DDIs remain unexplored clinically or cannot be studied due to ethical constraints. In most cases, the evaluation of DDIs is supported only by the individual judgment of the prescriber or expert opinion. Computer modelling tools can support the prediction of potential DDIs, providing a quantitative estimate of DDI magnitude. The aim of this study was to develop a quantitative algorithm for the prediction of enzymatic mediated induction DDIs of antiretrovirals (ARV).

**Methods:** In vitro drug metabolism data for 73 drugs across multiple disease areas were integrated to provide a comprehensive description of the mechanisms underpinning induction DDIs, including: in vitro drug metabolism and pharmacokinetics (DMPK) data, transporter specificity and induction potential of metabolic enzymes. For each DDI substrate an in vitro metabolism metric (IVMM) was calculated through the integration of the fractions metabolised (F<sub>m</sub>) by each hepatic enzyme multiplied by the inducer effect (E) for the corresponding enzyme isoform. Rifampicin was selected as a DDI perpetrator and a multiple linear regression model was generated to identify predictors of the DDI magnitude.

**Results:** The predicted area under the curve (AUC) ratios (with vs without rifampicin) obtained in our model were in agreement with the AUC ratios observed in clinical studies (Figure 1). Three independent in vitro variables were retained: IVMM, fraction unbound in plasma (F<sub>u</sub>) and substrate specificity for OATP1B1 transporter. All ARV (n = 11) DDI predictions were within 2-fold of observed clinical data and yielded a mean absolute error (MAE) of 0.11±0.09. Of all 73 drugs included in the algorithm, 42%, 70% and 88% were within 1.25-fold (0.8-1.25), 1.5-fold (0.66-1.5) and 2-fold (0.5-2) of the clinical data, respectively.

**Conclusion:** Management of DDIs in PLWH is challenging, especially in an ageing cohort with accumulating multiple comorbidities and polypharmacy. This model provides a fit-for-purpose tool to predict potential DDIs, utilising accessible in vitro data which could prove advantageous in early drug development and potentially help facilitate a more rational design of clinical studies evaluating the risk of toxicity and loss of efficacy associated with DDIs.



**Figure 1.** Predicted versus observed area under the curve (AUC) ratio for orally administered drugs (with vs without rifampicin). The solid black line represents the identity line, the dotted lines represent the 80-120% margins, the dashed lines represent the 66% and 150% margins and the grey lines represent the 50% and 200% margins.

### 366 EXOGENOUS HORMONE PHARMACOKINETICS IN TRANSGENDER ADOLESCENTS RECEIVING ORAL TDF/FTC

**Jenna L. Yager**<sup>1</sup>, Kristina Brooks<sup>1</sup>, Jennifer Brothers<sup>2</sup>, Daniel Reirden<sup>3</sup>, Meena Malhotra<sup>2</sup>, Carrie Glenn<sup>3</sup>, Kathleen Mulligan<sup>4</sup>, Raphael J. Landovitz<sup>2</sup>, Lucas Ellison<sup>1</sup>, Lane Bushman<sup>1</sup>, Jennifer Kiser<sup>1</sup>, Peter Anderson<sup>1</sup>, Sybil Hosek<sup>2</sup>

<sup>1</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>2</sup>Stroger Hospital of Cook County, Chicago, IL, USA, <sup>3</sup>Children's Hospital Colorado, Aurora, CO, USA, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA, <sup>5</sup>University of California Los Angeles, Los Angeles, CA, USA

**Background:** Transgender women (TW) and transgender men (TM) are at an increased risk of HIV infection, and would therefore benefit from the use of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) as pre-exposure prophylaxis (PrEP). Although there are increasing data available regarding the pharmacokinetics of TDF/FTC among TW, limited data exist for TM and adolescents. This lack of information is a major acceptability concern for these populations. This study assessed whether estradiol pharmacokinetics in TW, and testosterone pharmacokinetics in TM were altered with daily PrEP use.

**Methods:** Adolescent TW and TM ages 15-24 years, who were HIV-uninfected and receiving a stable cSH dose for ≥ 1 month or 3 consecutive doses, were enrolled. Participants received directly observed daily TDF/FTC for 30 days. Serum was collected for estradiol (TW) or testosterone (TM) concentrations at baseline (5-7 timepoints, dependent upon cSH dosing schedule) and after 2-3 weeks of daily TDF/FTC dosing. Estradiol and total testosterone were quantified using LC-MS/MS and free testosterone with equilibrium dialysis (Brigham Research Assay Core Laboratory, Boston, MA). Area under the curve (AUC) and maximum concentration (C<sub>max</sub>) at baseline and on PrEP were calculated using noncompartmental methods. Results were log-transformed and compared using a paired t-test.

**Results:** Twenty-four TM and 25 TW were included. Testosterone was received intramuscularly by 12 (50%) TM and subcutaneously by 12 TM (50%). Estrogen was received orally by 13 (52%) TW and intramuscularly by 12 TW (48%). Eighteen (72%) TW were also receiving spironolactone. For TM, median (range) age was 21 (17-24) years, creatinine clearance (CrCl) was 101.5 (71-279) ml/min, and weight was 58.9 (47.8-129.5) kg. For TW, median (range) age was 20 (16-24) years, CrCl was 129.9 (76.2-200) ml/min, and weight was 65.7 (49.2-90.8) kg. Geometric mean (GM) AUC and C<sub>max</sub> free testosterone, total testosterone, and estradiol at baseline and on TDF/FTC are displayed in Table 1.

**Conclusion:** TDF/FTC among HIV-uninfected adolescents did not significantly alter serum estradiol pharmacokinetics in TW, or free and total testosterone pharmacokinetics in TM. These data should be reassuring to persons in the transgender community with concerns about cSH during PrEP.

**Table 1.** Geometric mean AUC<sub>last</sub> and C<sub>max</sub> serum estradiol and testosterone

|  | Baseline<br>GM (95% CI)      | On PrEP<br>GM (95% CI)       | GMR<br>(95% CI)         | P      |
|--|------------------------------|------------------------------|-------------------------|--------|
| <b>Estradiol (N=25 transgender women)</b>        |                              |                              |                         |        |
| AUC <sub>last</sub><br>(h*pg/mL)                 | 9416<br>(4115, 21,547)       | 8160<br>(3662, 18,182)       | 0.867<br>(0.727, 1.034) | 0.1064 |
| C <sub>max</sub><br>(pg/mL)                      | 334<br>(221, 507)            | 284<br>(183, 440)            | 0.849<br>(0.651, 1.107) | 0.2148 |
| <b>Total Testosterone (N=24 transgender men)</b> |                              |                              |                         |        |
| AUC <sub>last</sub><br>(h*ng/dL)                 | 111,783<br>(96,490, 129,501) | 102,038<br>(84,258, 123,569) | 0.913<br>(0.805, 1.035) | 0.1479 |
| C <sub>max</sub><br>(ng/dL)                      | 812.7<br>(708, 933)          | 738.6<br>(616, 886)          | 0.909<br>(0.804, 1.027) | 0.1191 |
| <b>Free Testosterone (N=24 transgender men)</b>  |                              |                              |                         |        |
| AUC <sub>last</sub><br>(h*ng/dL)                 | 4003<br>(3377, 4746)         | 3515<br>(2785, 4438)         | 0.878<br>(0.744, 1.036) | 0.1185 |
| C <sub>max</sub><br>(ng/dL)                      | 31.1<br>(26.6, 36.4)         | 27.6<br>(22.0, 34.6)         | 0.887<br>(0.737, 1.068) | 0.1944 |

### 367 TFV-DP AND FTC-TP IN PBMC AMONG TRANSGENDER ADOLESCENTS RECEIVING DAILY TDF/FTC

**Jenna L. Yager**<sup>1</sup>, Kristina Brooks<sup>1</sup>, Jennifer Brothers<sup>2</sup>, Daniel Reirden<sup>3</sup>, Meena Malhotra<sup>2</sup>, Carrie Glenn<sup>3</sup>, Kathleen Mulligan<sup>4</sup>, Raphael J. Landovitz<sup>2</sup>, Bethany Johnson<sup>1</sup>, Lucas Ellison<sup>1</sup>, Lane Bushman<sup>1</sup>, Jennifer Kiser<sup>1</sup>, Peter Anderson<sup>1</sup>, Sybil Hosek<sup>2</sup>

<sup>1</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>2</sup>Stroger Hospital of Cook County, Chicago, IL, USA, <sup>3</sup>Children's Hospital Colorado, Aurora, CO, USA, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA, <sup>5</sup>University of California Los Angeles, Los Angeles, CA, USA

**Background:** Transgender women (TW) and transgender men (TM) have historically been underrepresented in pre-exposure prophylaxis (PrEP) clinical

trials. Recently, a few studies have sought to address a potential drug-drug interaction between PrEP and cross-sex hormone therapy (csHT), but data remain limited, particularly among adolescent transgender individuals and TM.

**Methods:** This was a prospective study conducted among adolescent TW and TM. Participants were HIV-uninfected, between 15–24 years of age, and were receiving a stable dose of csHT. They received 30 days of directly observed (DOT) daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC). PBMC were collected weekly for 4 weeks, at random times post-dose, and after 2–3 weeks of dosing, PBMC were collected at 0 (pre-dose), 4, and 24-hours. Intracellular tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) were determined using LC-MS/MS. Average TFV-DP and FTC-TP in PBMC were calculated using noncompartmental methods. Results were then log-transformed and compared between TM and TW, and compared against TFV-DP and FTC-TP from historical DOT cohorts.

**Results:** Fifty participants (24 TM, 26 TW) were included in this analysis. Among TW vs. TM, mean (SD) age (20 [2.5] vs. 20 [2.3] years), CrCl (136 [34.4] vs. 117 [48.4] ml/min), and weight (69 [11.9] vs. 69 [21.4] kg) were similar. Geometric mean Cavg TFV-DP and FTC-TP in PBMC are listed in the table. TM had 34% higher TFV-DP in PBMC vs. TW (GMR [95% CI]: 1.34 [1.002, 1.796],  $p=0.0485$ ) and 56% higher FTC-TP in PBMC vs. TW (GMR [95% CI]: 1.44 [1.14, 1.83],  $p=0.0032$ ). For comparison, values of TFV-DP and FTC-TP from historical DOT studies with 100% adherence ranged from 36.3–71.2 fmol/10<sup>6</sup> cells and 2.2–5.34 pmol/10<sup>6</sup> cells.

**Conclusion:** TM had higher TFV-DP and FTC-TP in PBMC vs. TW, consistent with previously-reported higher plasma TFV and FTC exposures. TFV-DP and FTC-TP in both populations were in line with previous DOT studies, suggesting no change in dosing is needed for PrEP utilization in TM and TW to achieve expected concentrations.

**Table 1.** Average concentrations of tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) at steady state

|  | N  | TFV-DP<br>(fmol/10 <sup>6</sup> cells) | FTC-TP<br>(pmol/10 <sup>6</sup> cells) |
|--|----|--|--|
| <b>TransPrEP Study Participants</b>                                  | 50 | 64.5 (55.5, 74.9)                      | 5.11 (4.49, 5.81)                      |
| Geometric mean (95% CI)  |    |  |  |
| Transgender Men  | 24 | 75.1 (62.9, 89.7)                      | 6.19 (5.30, 7.22)                      |
| Transgender Women  | 26 | 56.0 (44.2, 70.9)                      | 4.28 (3.56, 5.16)                      |
| <b>Historical Reference from Past DOT Studies (range of medians)</b> | 63 | 36.3–71.2                              | 2.2–5.34                               |

Past DOT studies include: HPTN 066 (Hendrix C, et al. *AIDS Res Hum Retroviruses*. 2016 Jan;32(1):32–43.), Shieh E, et al. *JIAS*. 2019;22:e25405., and DOT-DBS (Yager J. Presented at: *International Workshop on Clinical Pharmacology of HIV, Hepatitis & Other Antiviral Drugs*. 2019 May; Noordwijk (NL).)

### 368 PHARMACOKINETICS OF 2 CONTRACEPTIVE IMPLANTS AMONG WOMEN ON RILPIVIRINE-BASED ART

**Shadia Nakalema**<sup>1</sup>, Catherine A. Chappell<sup>2</sup>, Michelle Pham<sup>3</sup>, Ritah Nakijoba<sup>1</sup>, Leah Mbabazi<sup>1</sup>, Pauline Byakika-Kibwika<sup>4</sup>, Julian Kaboggoza<sup>1</sup>, Stephen I. Walimbwa<sup>1</sup>, Jeffrey Jeppson<sup>3</sup>, Lee Winchester<sup>3</sup>, Marco Siccardi<sup>5</sup>, Courtney V. Fletcher<sup>3</sup>, Kimberly K. Scarsi<sup>3</sup>, Mohammed Lamorde<sup>3</sup>

<sup>1</sup>Infectious Diseases Institute, Kampala, Uganda, <sup>2</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>3</sup>University of Nebraska Medical Center, Omaha, NE, USA, <sup>4</sup>Makerere University College of Health Sciences, Kampala, Uganda, <sup>5</sup>University of Liverpool, Liverpool, UK

**Background:** Subdermal progestin-releasing implants, containing either etonogestrel (ENG) or levonorgestrel (LNG), are highly effective, long-acting, reversible contraceptive options. EFV-based ART significantly reduces the ENG and LNG exposure from both available implants, contributing to contraceptive failures. Alternative implant-ART combinations are needed but have not been widely evaluated. Our objective was to characterise the pharmacokinetics (PK) of ENG and LNG, each released from a subdermal implant, over 24 weeks in women with HIV on rilpivirine (RPV)-based ART.

**Methods:** Two separate, parallel group, non-randomised, PK studies evaluating either ENG (ENG study) or LNG (LNG study) were conducted in women receiving RPV-based ART. Participants were aged 18 to 45 years and virologically suppressed on EFV-based ART for at least 12 months prior to switching to RPV 25mg daily plus two NRTIs. A washout period of six-weeks occurred after ART switch, and before implant insertion. A 68mg ENG implant (n=28) or a 150mg LNG implant system (n=30) was inserted on day 0. Plasma was collected on day 0 and at weeks 1, 4, 12 and 24 post-insertion; week 24 was the primary endpoint. ENG and LNG concentrations in plasma were measured by a validated LC-MS/MS method, and compared to historical control groups of women with HIV from the same clinic, but not yet on ART (ENG control n=20; LNG

control=17), by geometric mean ratio (GMR; RPV group:control group) and 90% confidence interval (CI). Adverse events (AEs) were collected at every study visit.

**Results:** All participants were Black African females. Both control groups had higher mean baseline body weight (66 and 69 kg) compared to the RPV groups (60 and 55 kg) for the ENG and LNG studies, respectively. ENG and LNG concentrations and associated comparison with historical data are indicated in the Table. At week 24, both ENG and LNG were modestly higher in the RPV group compared to each control group [ENG: 1.18 (1.00 – 1.35); LNG: 1.28 (0.99 – 1.52)]. One participant in the ENG study had grade 3 weight gain; no grade 3 or greater AEs were reported in the LNG study or in either control group.

**Conclusion:** Over the 24-week study period, concentrations of ENG and LNG from a contraceptive implant were modestly higher, but not clinically different in women receiving RPV-based ART compared to the historical control groups. Our results support that both the ENG and LNG implant are effective contraceptive options for women receiving RPV-based ART.

| Week | Etonogestrel 68mg subdermal implant            |   |                             | Levonorgestrel 150mg subdermal implant         |   |                             |
|------|--|---|-----------------------------|--|---|-----------------------------|
|      | Historic control (n=20)<br>Median (IQR); pg/mL | RPV-based ART (n=28)<br>Median (IQR); pg/mL | GMR (90% CI)<br>RPV:Control | Historic control (n=17)<br>Median (IQR); pg/mL | RPV-based ART (n=30)<br>Median (IQR); pg/mL | GMR (90% CI)<br>RPV:Control |
| 1    | 913.5<br>(720, 793)                            | 1025<br>(807, 1337.5)                       | 1.23<br>(1.02 – 1.40)       | 1073<br>(744, 1586)                            | 1430<br>(952, 1700)                         | 1.29<br>(0.92 – 1.58)       |
| 4    | 487.5<br>(408, 572)                            | 612<br>(541, 737)                           | 1.26<br>(1.06 – 1.44)       | 741<br>(472, 787)                              | 768<br>(623, 1100)                          | 1.26<br>(0.98 – 1.48)       |
| 12   | 410.5<br>(365, 505)                            | 514.5<br>(431, 609)                         | 1.16<br>(0.99 – 1.31)       | 598<br>(417, 816)                              | 743<br>(566, 952)                           | 1.23<br>(0.93, 1.47)        |
| 24   | 383.5<br>(278, 440)                            | 412<br>(366, 502)                           | 1.18<br>(1.00 – 1.35)       | 501<br>(366, 706)                              | 680<br>(544, 944)                           | 1.28<br>(0.99 – 1.52)       |

### 369 DRUG INTERACTIONS WITH ONCE-DAILY B/F/TAF IN COMBINATION WITH ONCE-WEEKLY RIFAPENTINE

**Priyanka Arora**<sup>1</sup>, Sean E. Collins<sup>1</sup>, Hal Martin<sup>1</sup>, Xu Zhang<sup>1</sup>, Lily Mak<sup>1</sup>, John Ling<sup>1</sup>, Polina German<sup>1</sup>

<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Bictegravir (BIC)/emtricitabine/tenofovir alafenamide (B/F/TAF) once-daily (QD) is approved as a first-line treatment for HIV-1 infection in adults and children weighing at least 25 kg. BIC is metabolized by uridine diphosphate-glucuronosyl transferase 1A1 and cytochrome P450 (CYP)3A. Rifapentine (RPT), an anti-tuberculosis (TB) agent used for the treatment of latent and active TB infection, is a strong inducer of CYP3A but with induction potency less than that of rifampin. This study evaluated the effect of once-weekly (QW) RPT administration on pharmacokinetics (PK) of B/F/TAF to assess their ability to be co-administered in patients with HIV and latent TB co-infection.

**Methods:** A Phase 1, open-label, 3-period, fixed sequence study was conducted in 30 HIV-negative volunteers. Participants received B/F/TAF (50/200/25mg) QD on Days 1–8 followed by a washout period from Days 9–14. Participants then received B/F/TAF QD on Days 15–30 with QW RPT (weight-based dosing) co-dosed on Days 15 and 22, and 12-hours before B/F/TAF on Day 29. Safety was assessed throughout the study. Intensive plasma sampling was performed on Days 8, 22, and 30 for determination of BIC, F, TAF and tenofovir (TFV; TAF metabolite) PK. BIC troughs were collected on Days 16–21 and 23–29 between RPT doses to examine time-course of induction. Drug interaction was assessed using the geometric least-squares mean ratios and corresponding 90% confidence intervals of the test versus reference treatments with no effect boundaries defined as (70%–143%).

**Results:** All treatments were well-tolerated. QW RPT decreased BIC C<sub>tau</sub> by ~40% on Day 22 (co-dose) and by ~57% on Day 30 (12-hr stagger). BIC C<sub>tau</sub> decline at the nadir was ~83%, occurring 3–4 days post RPT dosing. Notably, BIC C<sub>tau</sub> did not rebound back to steady state concentrations between RPT doses. 12-hour staggered administration of RPT resulted in a more pronounced decline in BIC C<sub>tau</sub> compared to its co-administration. No clinically relevant changes in the PK of F, TAF, and TFV were observed upon administration with RPT (Table 1). **Conclusion:** Significant decline in BIC C<sub>tau</sub> is observed following administration of B/F/TAF with RPT. The use of QW RPT in combination with B/F/TAF is not recommended.

**Table 1. Summary of Pharmacokinetic Parameter Estimates across Study Treatments**

| PK Parameter Mean (% CV)      | QD B/F/TAF alone (Day 8; N=29) | QD B/F/TAF + QW RPT (co-dose; Day 22; N=29) | QD B/F/TAF + QW RPT (12-hr stagger; Day 30; N=28) | Day 22 vs Day 8 %GLSM (90% CI) | Day 30 vs Day 8 %GLSM (90% CI) |
|-------------------------------|--------------------------------|---|---|--------------------------------|--------------------------------|
| <b>Bictegravir</b>            |                                |   |   |                                |                                |
| C <sub>max</sub> (ng/mL)      | 6870 (16.3)                    | 6880 (16.9)                                 | 6590 (16.6)                                       | 100 (95.5, 105)                | 95.9 (91.8, 100)               |
| AUC <sub>0-24</sub> (h*ng/mL) | 96100 (23.3)                   | 81400 (17.9)                                | 70800 (18.3)                                      | 85.5 (81.3, 89.8)              | 74.1 (70.2, 78.3)              |
| C <sub>min</sub> (ng/mL)*     | 2510 (28.1)                    | 1520 (26.6)                                 | 1080 (27.2)                                       | 60.4 (56.3, 64.7)              | 42.5 (39.1, 46.2)              |
| <b>Emtricitabine</b>          |                                |   |   |                                |                                |
| C <sub>max</sub> (ng/mL)      | 1860 (19.6)                    | 1960 (18.0)                                 | 1940 (20.0)                                       | 106 (99.1, 113)                | 105 (97.5, 112)                |
| AUC <sub>0-24</sub> (h*ng/mL) | 9690 (14.6)                    | 11000 (14.6)                                | 11300 (13.6)                                      | 113 (110, 117)                 | 117 (114, 120)                 |
| C <sub>min</sub> (ng/mL)      | 72.5 (21.5)                    | 66.0 (31.8)                                 | 86.5 (22.4)                                       | 88.9 (82.6, 95.5)              | 119 (115, 124)                 |
| <b>Tenofovir alafenamide</b>  |                                |   |   |                                |                                |
| C <sub>max</sub> (ng/mL)      | 174 (42.2)                     | 231 (44.6)                                  | 211 (71.4)  | 131 (113, 152)                 | 109 (89.4, 133)                |
| AUC <sub>0-24</sub> (h*ng/mL) | 255 (39.2)                     | 324 (49.2)                                  | 288 (45.1)  | 112 (93.9, 134)                | 98.4 (91.8, 105)               |
| <b>Tenofovir</b>              |                                |   |   |                                |                                |
| C <sub>max</sub> (ng/mL)      | 14.9 (18.7)                    | 13.3 (19.2)                                 | 12.1 (18.1)                                       | 89.3 (84.9, 93.9)              | 81.5 (77.6, 85.6)              |
| AUC <sub>0-24</sub> (h*ng/mL) | 224 (16.6)                     | 195 (16.6)                                  | 197 (17.3)  | 87.2 (84.6, 89.8)              | 88.0 (85.0, 91.0)              |
| C <sub>min</sub> (ng/mL)      | 7.58 (19.4)                    | 6.60 (15.8)                                 | 6.84 (17.3)                                       | 87.4 (84.1, 90.9)              | 90.5 (86.7, 94.5)              |

\*Mean BIC C<sub>min</sub> reached the nadir on Day 25 (~3 days post the 2<sup>nd</sup> dose of RPT) corresponding to %GLSM (90% CI) of 17.1 (15.6, 18.8) as compared to B/F/TAF-QD alone (Day 8; reference)

B/F/TAF= bictegravir/emtricitabine/tenofovir alafenamide; RPT= rifapentine; GLSM= geometric least-squares mean; CI= confidence interval; CV= coefficient of variation; QD= once-daily; QW= once-weekly

Data is shown to 3 significant digits

**Table 1 Pharmacokinetic parameters of dolutegravir among 2 doses (dolutegravir 50 mg once daily with food and dolutegravir 50 mg twice daily) in rifampicin treated TB/HIV coinfecting patients**

|                                | DTG 50 mg OD with food + 2NRTIs (n=12) | DTG 50 mg BID + 2NRTIs (n=16) | GMR (90%CI)      | P-value |
|--------------------------------|--|-------------------------------|------------------|---------|
| C <sub>max</sub> (ug/mL)       | 2.07 (1.39-3.08)                       | 2.46 (2-3.02)                 | 0.84 (0.61-1.17) | 0.38    |
| AUC <sub>0-24</sub> (ug-hr/mL) | 19.98 (14.04-28.44)                    | 18.71 (14.54-24.07)           | 1.07 (0.77-1.49) | 0.74    |
| C <sub>min</sub> (ug/mL)       | 0.12 (0.08-0.18)                       | 0.39 (0.23-0.65)              | 0.30 (0.26-0.36) | <0.001  |
| C <sub>min</sub> > 0.064 ug/mL | 10 (83%)                               | 15 (94%)                      | -                | 0.16    |
| T <sub>max</sub> (hr)*         | 3.23 (1.08-6.25)                       | 2.15 (1.03-6.33)              | -                | 0.19    |
| t <sub>1/2β</sub> (hr)**       | 5.15 (4.05-6.87)                       | 4.77 (4.03-6.19)              | -                | 0.63    |
| CL <sub>cr</sub> /F (L/hr)     | 2.5 (1.76-3.56)                        | 2.67 (2.08-3.44)              | 0.94 (0.7-1.30)  | 0.74    |

The data is described with Geometric mean (90%CI), GMR: Geometric mean ratio

\*Median (minimum-maximum); \*\*Median (IQR); C<sub>min</sub>: minimum concentration; C<sub>max</sub>: maximum concentration; AUC<sub>0-24</sub>: area under curve; T<sub>max</sub>: time to maximum concentration; t<sub>1/2β</sub>: half-life; CL<sub>cr</sub>/F: oral clearance

**370 EFFICACY AND PK OF DOLUTEGRAVIR 50 mg QD WITH FOOD VERSUS 50 mg BID WITH RIFAMPICIN**

**Thornthun Ueaphongsukkit**<sup>1</sup>, Sivaporn Gatechompol<sup>2</sup>, Jiratchaya Sophonphan<sup>3</sup>, Stephen J. Kerr<sup>4</sup>, Hay Mar Su Lwin<sup>3</sup>, Win Min Han<sup>3</sup>, Sasiwimol Ubolyam<sup>3</sup>, Prachya Chaiyahong<sup>3</sup>, Charnnarong Phothidokmai<sup>3</sup>, Yong Soon Cho<sup>5</sup>, Jae Gook Shin<sup>5</sup>, Anchalee Avihingsanon<sup>2</sup>, for the HIV-NAT 254 Study  
<sup>1</sup>Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, <sup>2</sup>Tuberculosis Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, <sup>3</sup>HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, <sup>4</sup>Biostatistics Excellence Centre, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, <sup>5</sup>Center for Personalized Precision Medicine of Tuberculosis, Inje University College of Medicine, Busan, Korea, Republic of

**Background:** Concurrent use of rifampicin (RIF) and dolutegravir (DTG) reduces DTG exposure, thus, DTG 50 mg twice-daily is currently recommended. Food increased DTG concentrations in healthy volunteers by 33 – 66%. We therefore investigated the effect of RIF on DTG exposure when dosed at 50 mg once daily with food, which would be more convenient than 50 mg twice daily in resource limited settings, where generic fixed dosed combination of TDF/ 3TC/DTG (TLD) is widely available.

**Methods:** We conducted a single-center, open-label study in Bangkok, Thailand. TB/HIV coinfecting adults, ART naive, stable on RIF containing regimen for drug-susceptible TB were randomly assigned to receive DTG 50 mg OD with food (study arm; TLD 1 pill/day) or DTG 50 mg twice-daily (control arm; TLD 1 pill plus additional DTG). Intensive PK was scheduled at week 4. Blood samples were collected pre-dose, 1, 2, 4, 6, 8, 12, and 24-hour post-dose (by study arm). HIV-RNA, liver and renal function tests were monitored. DTG concentrations were determined by validated LC-MS/MS. PK parameters were estimated (nonparametric; WinNonLin). The primary endpoint was DTG geometric mean ratios (GMRs) of DTG 50 mg QD vs DTG 50 mg BID (90%CI) and percent of participants with DTG minimum concentrations (C<sub>min</sub>) above the required protein-adjusted 90% inhibitory concentration (IC<sub>90</sub>) of 0.064 ug/mL.

**Results:** Totally 12 study arm and 16 control arm participants completed PK analysis. The majority were male (86%); with median age 32 years, and median body weight 57.5 kg. At baseline, median CD4 was 201 (IQR 46-304) cells/μL and median HIV RNA was 4.9 (IQR 3.6-5.6) log<sub>10</sub> copies/mL; 43% had HIV-RNA >100,000 copies/mL. GMR (90%CI) maximum concentration (C<sub>max</sub>) and area under curve (AUC<sub>0-24</sub>) not within the bioequivalence range of 0.8-1.25: 0.84 (0.61-1.17) and 1.07 (0.77-1.49), respectively (Table 1). C<sub>min</sub> GMR in the study arm was 0.3 (0.26-0.36), but 83% and 94% of study and control arm participants had DTG C<sub>min</sub> >0.064 ug/mL, respectively. At week 12, 83.3% and 81.3% of participants in study arm and control arm, respectively had HIV-RNA <40 copies/mL. Both arms were well-tolerated.

**Conclusion:** Although there were substantial reductions in DTG concentrations when co-administered with RIF, C<sub>min</sub> levels were mostly above the protein-binding-adjusted IC<sub>90</sub> of 0.064 ug/mL and majority of participants (>80%) had VL suppression at week 12.

**371 INTRACELLULAR DISPOSITION OF DARUNAVIR/RITONAVIR AND DOLUTEGRAVIR WITH RIFAMPIN**

**Amedeo De Nicolò**<sup>1</sup>, Andrea Calcagno<sup>1</sup>, Ilaria Motta<sup>1</sup>, Elisa De Vivo<sup>1</sup>, Antonio D'Avolio<sup>1</sup>, Giovanni Di Perri<sup>1</sup>, Lubbe Wiesner<sup>2</sup>, Ismael Ebrahim<sup>2</sup>, Gary Maertens<sup>2</sup>, Catherine Orrell<sup>2</sup>, Helen McIlleron<sup>2</sup>

<sup>1</sup>University of Turin, Turin, Italy, <sup>2</sup>University of Cape Town, Cape Town, South Africa

**Background:** Darunavir and ritonavir (DRV/r) are victims of drug-drug interactions (DDI) with strong cytochrome inducers, such as rifampin (RIF). Recently our group showed that doubling DRV/r dose did not compensate for the RIF-induced decrease in DRV exposure. The impact of similar DDIs within Peripheral Blood Mononuclear Cells (PBMC) is still unknown. Therefore, in the same context, we investigated the intra-PBMC pharmacokinetics of DRV/r, dolutegravir (DTG) and RIF.

**Methods:** People living with HIV were enrolled in a dose-escalation cross-over study (NCT03892161), with treatment periods of 7 days each. Patients started with DRV/r 800/100 mg QD, then RIF (600-750 mg QD) and DTG (50 mg BD) were added, RTV dose was increased to 200 mg, then they received either DRV/r 800/100 BD and then 1600/200 QD or vice versa. Last, RIF was withdrawn. Plasma and intra-PBMC concentrations of each drug were measured through validated LC-MS/MS methods, at the end of each treatment period (steady-state) at the end of dosing interval (C<sub>trough</sub>), and at 2-6 h (start and after DRV/r dose escalations). Seventeen patients were enrolled in this study but, due to high incidence of liver toxicity only 4 patients completed the protocol.

**Results:** Overall plasma and intra-PBMCs C<sub>trough</sub> and AUC<sub>0-24</sub> are showed in table 1 for each period. In the patients who completed the protocol, after the addition of RIF, intra-PBMC DRV C<sub>trough</sub> dropped significantly (P = 0.039) from a median starting value of 215 ng/mL (IQR 144 – 374) to 119 ng/mL (IQR 13 – 694) and 68 ng/mL (IQR 16 – 164) for 800/100 BD and 1600/200 QD dosages, respectively. Differences were slighter at 2-6 hours (P = 0.114). RIF addition and dose escalation was associated with a significant increase in the intra-PBMC/plasma ratio for DRV, from a median starting value of 0.17 (IQR 0.09 – 0.26) to 0.23 (IQR 0.20 – 0.26) and 0.28 (IQR 0.21 – 0.41) for 800/100 BD and 1600/200 QD regimens, respectively. DTG and RIF intra-PBMC concentrations were similar to the ones reported in literature. DTG intra-PBMC/plasma C<sub>trough</sub> ratio showed a slight increase (P = 0.068) between DRV/r BD and QD double doses: median 0.24 (IQR 0.21 - 0.25) and 0.29 (IQR 0.26 – 0.32), respectively.

**Conclusion:** The observed data suggest that the relative intracellular disposition of DRV increases with RIF; DTG intra-PBMCs exposure seems similar to what reported in patients not receiving RIF. Considering the intra-PBMCs concentrations may be useful for predicting the clinical relevance of DDIs with strong inducers.

**Table 1:** Summary of PK data in plasma and PBMC for each drug (C<sub>trough</sub> data are described only for DRV) at the end of each treatment period (steady-state); data are shown as median values (interquartile ranges). N.a. = not applicable; n.d. = not determinable; n.c. = not computable.

|  | DRV/RTV<br>800/100 QD<br>(n = 17) | DRV/RTV<br>800/100 QD + RIF + DTG<br>(n = 36) | DRV/RTV<br>800/200 QD + RIF + DTG<br>(n = 10) | DRV/RTV<br>800/100 QD + DTG + RIF<br>(n = 4) | DRV/RTV<br>1600/200 QD + DTG + RIF<br>(n = 4) | Last DRV/r<br>regimen + DTG<br>without RIF<br>(n = 9) |
|--|-----------------------------------|---|---|--|---|---|
| DRV AUC <sub>0-24</sub> Plasma (h·ng/mL)   | 92461 (39655 – 197735)            | n.a.  | n.a.  | 45532 (27298 – 118740)                       | 34695 (8025 – 69029)                          | -   |
| DRV AUC <sub>0-24</sub> PBMC (h·ng/mL)     | 17503 (10975 – 34876)             | n.a.  | n.a.  | 11100 (8756 – 31100)                         | 10087 (8292 – 21726)                          | -   |
| DRV C <sub>trough</sub> plasma (ng/mL)     | 2370 (839 – 7135)                 | 37 (19 – 53)                                  | 86 (45 – 245)                                 | 536 (27 – 3540)                              | 126 (31 – 1244)                               | 3550 (1660 – n.c.)                                    |
| DRV C <sub>trough</sub> PBMC (ng/mL)       | 361 (158 – 577)                   | 10 (n.d. – 13)                                | 25 (12 – 67)                                  | 112 (18 – 820)                               | 31 (12 – 333)                                 | 830 (525 – n.c.)                                      |
| DRV PBMC/Plasma trough concentration ratio | 0.11 (0.08 – 0.16)                | 0.26 (0.21 – 0.34)                            | 0.25 (0.23 – 0.29)                            | 0.21 (0.10 – 0.57)                           | 0.34 (0.18 – 0.45)                            | 0.24 (0.23 – n.c.)                                    |
| RTV AUC <sub>0-24</sub> Plasma (h·ng/mL)   | 6069 (3635 – 7853)                | n.a.  | n.a.  | 6642 (2098 – 9779)                           | 6517 (2938 – 8996)                            | -   |
| RTV AUC <sub>0-24</sub> PBMC (h·ng/mL)     | 9829 (8550 – 12410)               | n.a.  | n.a.  | 13606 (6444 – 21352)                         | 14475 (7179 – 18793)                          | -   |
| DTG AUC <sub>0-24</sub> Plasma (h·ng/mL)   | n.a.                              | n.a.  | n.a.  | 31646 (23033 – 97240)                        | 30967 (21933 – 41292)                         | -   |
| DTG AUC <sub>0-24</sub> PBMC (h·ng/mL)     | n.a.                              | n.a.  | n.a.  | 14889 (10813 – 17636)                        | 12807 (11364 – 24391)                         | -   |
| DTG C <sub>trough</sub> Plasma (ng/mL)     | n.a.                              | 1245 (524 – 1727)                             | 1248 (524 – 1727)                             | 1431 (120 – 1911)                            | 962 (669 – 2758)                              | 1382 (1215 – n.c.)                                    |
| DTG C <sub>trough</sub> PBMC (ng/mL)       | n.a.                              | 223 (152 – 378)                               | 274 (145 – 389)                               | 363 (29 – 444)                               | 251 (204 – 856)                               | 344 (290 – n.c.)                                      |

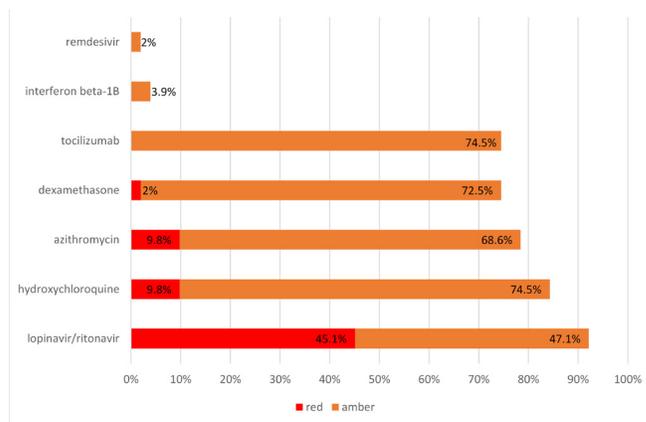


Figure 1. Proportion of patients with potential co-med/COVID-med drug-drug interactions (n=51)

## 372 POTENTIAL DRUG-DRUG INTERACTIONS IN HOSPITALIZED COVID-19 PATIENTS (CATCO-DDI)

Alice Tseng<sup>1</sup>, Nancy Sheehan<sup>2</sup>, Kendra Hewlett<sup>3</sup>, Alison Y. Wong<sup>2</sup>, Maria Kulikova<sup>4</sup>, Bryan Coburn<sup>4</sup>, Rob Fowler<sup>5</sup>, Matthew P. Cheng<sup>2</sup>, Srinivas Murthy<sup>6</sup>

<sup>1</sup>Toronto General Hospital, Toronto, Canada, <sup>2</sup>McGill University Health Centre, Montreal, Canada, <sup>3</sup>University of Toronto, Toronto, Canada, <sup>4</sup>Toronto General Research Institute, Toronto, Canada, <sup>5</sup>Sunnybrook Research Institute, Toronto, Canada, <sup>6</sup>BC Children's Hospital Research Institute, Vancouver, Canada

### Background:

Therapies for managing COVID-19 disease may interact with other drugs, particularly in hospitalized patients with comorbidities. We characterized the prevalence of potential drug-drug interactions (DDIs) between investigational/approved medications for managing COVID-19 (COVID-meds) and co-medications (co-meds) in hospitalized COVID-19 patients.

### Methods:

Multicentre retrospective observational study of hospitalized COVID-19 patients screened for the CATCO arm of the SOLIDARITY trial between 1-Apr-20 and 15-Sep-20. Patients' co-meds at screening were assessed for potential DDIs with the following COVID-meds: hydroxychloroquine (HQ), lopinavir/ritonavir (LPV), remdesivir (REM), dexamethasone (DEX), azithromycin (AZ), interferon beta-1B (IFN) and tocilizumab (TOC). The Liverpool-COVID DDI website and Lexicomp were used to identify and characterize DDI severity (red: do not co-administer, amber: potential clinically significant) and potential clinical impact. QT prolongation risk was assessed with the Tisdale risk score. The primary outcome was the prevalence of subjects with  $\geq 1$  potential clinically significant (red/amber) DDI between each COVID-med and co-med. Secondary outcomes included DDI severity and potential clinical impact and prevalence of DDIs between co-meds. Descriptive statistics are presented as medians (range) or proportions.

### Results:

Data from 51 patients are available: 61% male, age 74 (44-95) years, number of comorbidities 6 (1-15), Tisdale risk score 6 (31.4% moderate risk, 11.8% high risk) and 10 (0-19) co-meds. LPV had the highest rate of potential DDIs (92.2%, 45% red, 3 DDIs per patient) with risk of increased co-med toxicity (most commonly psychotropics, anticoagulants/antiplatelets), while REM and IFN had the least (2% and 9.6%, respectively). Most patients (75%) had  $\geq 1$  DEX DDI (primarily amber, 1 per patient) with risk of increased co-med toxicity (Figure 1). The most common DDIs with HQ and AZ involved increased risk of QTc prolongation. Lexicomp identified co-med/co-med DDIs in 62.7% of patients (88% amber, 12% red) most often with increased risk of drug toxicity, commonly involving heparin/LMWH, opioids and antiplatelets. Over one-third (35%) of patients were deemed ineligible for CATCO at screening due to DDIs with LPV.

### Conclusion:

Hospitalized COVID-19 patients are at high risk of DDIs with many investigational or approved COVID medications. Routine DDI screening is recommended, ideally using both general and COVID-specific DDI resources.

## 373 CABOTEGRAVIR PPK SIMULATION TO INFORM Q2M STRATEGIES FOLLOWING DOSING INTERRUPTIONS

Kelong Han<sup>1</sup>, Mark Baker<sup>2</sup>, William R. Spreen<sup>3</sup>, Susan L. Ford<sup>4</sup>

<sup>1</sup>GlaxoSmithKline, Collegeville, PA, USA, <sup>2</sup>ViiV Healthcare, Nyon, Switzerland, <sup>3</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>4</sup>GlaxoSmithKline, Research Triangle Park, NC, USA

**Background:** Cabotegravir (CAB) is an integrase strand transfer inhibitor formulated as long-acting (LA) injection for treatment and prevention of HIV, and as tablet for oral lead-in and bridging therapy for LA dose interruptions. CAB LA administered with rilpivirine (RPV) LA is a 2-drug regimen for HIV treatment with proven efficacy following LA injections monthly and every 2 months (Q2M). Population pharmacokinetic (PPK) modeling and simulation was performed to inform strategies for managing dosing interruptions of the Q2M regimen. RPV simulations are presented separately.

**Methods:** The CAB PPK model described data following oral and LA administration adequately. Simulations of 500 virtual subjects (female:male=1:1) were performed using covariate sampling with replacement from the PPK dataset. One- to 12-week delays in dosing of the 2nd, 3rd, and 4th injection were simulated. Oral bridging simulations were performed with oral dosing starting at the time of the missed injection for a duration of 1-3 months when CAB LA dosing was resumed. Results were compared to simulated uninterrupted profiles wherein 95% of subjects maintain concentrations above 0.65 µg/mL (benchmark in Phase 3 HIV treatment studies).

**Results:** The proportion of subjects above benchmark was predicted to fall temporarily to as low as 92.8% (<95% for  $\leq 1$  week) following a 1-week delay, 90% following a 2-week delay, and 10% with a 12-week delay (Table). Delays of >4 weeks have a greater impact on the 2nd injection than later injections. Oral bridging with CAB 30mg once daily starting at the time of a planned missed injection is predicted to provide exposures within ranges observed in Phase 3 studies.

**Conclusion:** Adherence to Q2M schedule is strongly recommended. When the 2nd, 3rd, or 4th injection is delayed, dosing delays of up to 1 week were predicted to have minimal impact, but longer delays may have a greater impact, particularly for the 2nd injection. Oral bridging provides therapeutic and safe exposures for planned interruptions in IM dosing. Regardless of oral bridging, simulations support: If injection is delayed by  $\leq 1$  month ( $\leq 2$  months between the 1st and 2nd injections or  $\leq 3$  months between subsequent injections): resume 3 mL injections Q2M as soon as possible; and if injection is delayed by >1 month (>2 months between the 1st and 2nd injections or >3 months between subsequent injections): reinstate Q2M regimen with a 3 mL injection followed by 3 mL Q2M 1 month after the resumed injection.

**Table. Predicted Proportion of Subjects (%) with CAB Trough Concentration Above the Phase 3 Benchmark of 0.65 µg/mL Following the Delayed Injection**

| Delayed Injection | CAB Trough Concentration                       | Length of Delay |                     |         |         |                      |                      |                      |                       |
|-------------------|--|-----------------|---------------------|---------|---------|----------------------|----------------------|----------------------|-----------------------|
|                   |  | No Delay        | 1 <sup>a</sup> Week | 2 Weeks | 3 Weeks | 4 <sup>b</sup> Weeks | 6 <sup>b</sup> Weeks | 8 <sup>b</sup> Weeks | 12 <sup>b</sup> Weeks |
| 2nd IM injection  | Trough prior to resuming the delayed injection | 95.0            | 93.6 (5)            | 91.4    | 86.2    | 77.4                 | 59.0                 | 33.4                 | 9.6                   |
|                   | Trough after resuming the delayed injection    | 95.6            | 94.8                | 94.2    | 94      | 92.8 / 96.2          | 92.2 / 96.2          | 91.8 / 96.2          | 91.2 / 96             |
| 3rd IM injection  | Trough prior to resuming the delayed injection | 95.6            | 92.8 (5)            | 90.4    | 86.6    | 81.6                 | 66.8                 | 53.6                 | 31.0                  |
|                   | Trough after resuming the delayed injection    | 94.6            | 94.2                | 93.6    | 93.4    | 93.2 / 96.6          | 92.8 / 96.6          | 92 / 96.6            | 91.6 / 96.2           |
| 4th IM injection  | Trough prior to resuming the delayed injection | 94.6            | 93.0 (7)            | 89.8    | 84.8    | 78.8                 | 66.6                 | 58.4                 | 41.0                  |
|                   | Trough after resuming the delayed injection    | 94.6            | 94.0                | 93.6    | 93.6    | 93.4 / 96.8          | 93 / 96.8            | 92.2 / 96.6          | 91.8 / 96.4           |

<sup>a</sup>Number in parenthesis indicates the number of days during which the proportion of subjects above benchmark was predicted to stay below 95%. <sup>b</sup>Trough after resuming the delayed injection is displayed as "without / with reinitiating the Q2M regimen". Without reinitiating the Q2M regimen, 3 mL of CAB is administered for the resumed injection, and then Q2M thereafter. With reinitiating the Q2M regimen, 3 mL of CAB is administered for the resumed injection, again one month later, and Q2M thereafter.

**374 IN SILICO PREDICTION OF LONG-ACTING CABOTEGRAVIR PK IN LIVER-IMPAIRED PATIENTS**

Nicolas Cottura<sup>1</sup>, Maiara C. Montanha<sup>1</sup>, Fazila S. Bunglawala<sup>1</sup>, Sandra Grañana-Castillo<sup>1</sup>, Hannah Kinvig<sup>1</sup>, Marco Siccardi<sup>1</sup>  
<sup>1</sup>University of Liverpool, Liverpool, UK

**Background:** Intramuscular (IM) long acting (LA) antiretrovirals can provide pharmacological options to simplify regimens and improve adherence. Currently, two IM LA drugs have been developed, rilpivirine (RPV) and cabotegravir (CBV), however the impact of liver impairment on their pharmacokinetics (PK) has not been fully elucidated. The aim of this project was to predict the PK of IM LA CBV in patients with liver impairment conditions using physiologically-based pharmacokinetic (PBPK) modelling.

**Methods:** A whole-body IM PBPK model was designed in Simbiology v.5.8.1 (MATLAB R2018b) and used to simulate 100 healthy and liver impaired adults aged 18-60 years. The model was assumed to be qualified if the simulated values were within 2-fold of the mean reported values, using the absolute average fold error (AAFE) approach as per convention. The model was validated using both oral (30mg QD) and IM administration (800mg followed by maintenance dose of 800mg 3 months later) clinical data on CBV. The PBPK model used first order kinetics to describe the IM LA drug release process. Virtual liver impaired patients were classified following the Child-Pugh (CP) score. Equations describing organ and tissue blood flows, plasma protein concentrations and hepatic metabolic enzyme changes were optimised according to each CP score.

**Results:** The CBV PBPK model successfully passed the validation criteria, as shown in Table 1. Predictions for the IM dose of CBV showed a decrease of 8, 23 and 50% for AUC, C<sub>trough</sub> and C<sub>max</sub> compared to healthy condition, respectively in CP-A, B and C conditions. A portion of the patients with CP-C liver impairment are predicted to have total plasma C<sub>trough</sub> below the PAIC90 (660 ng/mL). However, the unbound CBV concentrations are predicted to be comparable to healthy individuals for all patients with liver impairment due to the increase of free drug fraction.

**Conclusion:** These data suggest that IM LA CBV may be used safely in patients with liver impairment, considering the overall steady-state and increment in unbound plasma concentrations. This approach could also be utilised for the prediction of risk related to altered PK for IM LA therapy in liver impaired patients as well as supporting the design of future clinical trials.

**Table 1. Pharmacokinetic summary of simulated Cabotegravir in healthy adults and adults with liver dysfunction.**

| Variables                    | CP Score  | Oral dose (OD) |       |                | Intramuscular (IM) |              |              |
|------------------------------|-----------|----------------|-------|----------------|--------------------|--------------|--------------|
|                              |           | Healthy        | CP-B  | Healthy        | CP-A               | CP-B         | CP-C         |
| AUC <sub>0-∞</sub> (ng·h/mL) | Observed  | 134            | 108   | 9,083          | -                  | -            | -            |
|                              | Predicted | 11,564         | 8,931 | 8,801          | 8,101              | 6,703        | 5,221        |
|                              | AAFE      | 1.159          | 1.209 | 1.032          | -                  | -            | -            |
| C <sub>max</sub> (ng/mL)     | Observed  | 3,540          | 2,880 | 3,287          | -                  | -            | -            |
|                              | Predicted | 3,171          | 3,057 | 3,750          | 3,472              | 2,894        | 2,264        |
|                              | AAFE      | 1.148          | 1.061 | 1.141          | -                  | -            | -            |
| Cl/F (L/h)                   | Observed  | 0.246          | 0.312 | -              | -                  | -            | -            |
|                              | Predicted | 0.259          | 0.336 | -              | -                  | -            | -            |
|                              | AAFE      | 1.055          | 1.077 | -              | -                  | -            | -            |
| C <sub>min</sub> (ng/mL)     | Observed  | -              | -     | 1,091 [7.637]* | -                  | -            | -            |
|                              | Predicted | -              | -     | 906 [6.349]*   | 832 [6.3232]*      | 685 [6.302]* | 531 [6.287]* |
|                              | AAFE      | -              | -     | 1.203          | -                  | -            | -            |

Data shown represent mean values. CP-A, B and C correspond to the Child-Pugh score. \* represents unbound concentration (ng/mL). AUC<sub>0-∞</sub>, area under the plasma concentration-time curve over 168 hours for the OD and 4,650 hours for the IM; C<sub>max</sub>, maximum plasma concentration; Cl/F, apparent clearance; C<sub>min</sub>, minimum plasma concentration between two IM administrations; -, not applicable

**375 PHARMACOKINETICS OF LENACAPAVIR, AN HIV-1 CAPSID INHIBITOR, IN HEPATIC IMPAIRMENT**

Vamshi Jogiraju<sup>1</sup>, Rebecca Begley<sup>1</sup>, Jason Hindman<sup>1</sup>, Steve West<sup>1</sup>, Emily Ho<sup>1</sup>, John Ling<sup>1</sup>, Polina German<sup>1</sup>

<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Lenacapavir (LEN, GS-6207), a potent, selective, first-in-class, multi-stage inhibitor of HIV-1 capsid function is in clinical development as a long acting agent to treat HIV-1 infection, supporting weekly (oral LEN) or less frequent dosing (subcutaneous LEN). In people living with HIV, LEN has shown potent antiviral activity and is well tolerated. This study was conducted to evaluate the effect of moderate hepatic impairment (HI) on the pharmacokinetics (PK) of oral LEN to inform dosing recommendations in patients with mild and moderate HI.

**Methods:** Participants with moderate HI (Child-Pugh Turcotte [CPT] classification B; score 7-9) and healthy controls (HC) matched for age (±10 years), sex, race and BMI (±15%) received a single oral dose of LEN 300 mg with food (moderate fat meal). Plasma PK was collected through Day 92 post dose; protein binding of LEN was assessed. Preliminary PK parameters were estimated using noncompartmental analysis, and geometric least squares mean (GLSM) ratios and 90% confidence intervals (CI) for AUCinf and C<sub>max</sub> were calculated (GLSM: HI:HC). Safety was evaluated throughout the study.

**Results:** 20 participants (N=10 with moderate HI and N=10 HC) were enrolled in the study. Preliminary LEN exposure, as assessed by AUCinf and C<sub>max</sub> was ~1.5-fold and ~2.6-fold higher respectively, in subjects with moderate HI, as compared to HC (Table 1). LEN plasma protein binding, median T<sub>max</sub> and t<sub>1/2</sub> were similar in both groups. Exploratory analyses indicated no relevant relationships between LEN exposure and CPT score or individual elements of CPT classification. Additionally, no correlation is observed between LEN exposure and subjects' weight or age. Study treatment was well tolerated. No participant experienced serious or Grade 3 or 4 treatment emergent adverse events. Four HI and one HC participants experienced Grade 3 or 4 lab abnormalities, none of which were considered clinically relevant. All Grade 3 or 4 laboratory abnormalities improved on the next visit and/or were preexisting.

**Conclusion:** LEN AUC and C<sub>max</sub> were 1.5- and 2.6-fold higher respectively, in moderately hepatically impaired participants as compared to healthy controls. Based on cumulative safety data in the LEN SC and oral clinical program, no dose adjustment of LEN is recommended in patients with mild to moderate hepatic impairment.

**Table 1. Preliminary PK data for LEN 300 mg (oral tablet) following single dose administration:**

| Parameter                      | HI (N=10)         | HC (N=10)*        | %GLSM Ratio (90%CI) |
|--------------------------------|-------------------|-------------------|---------------------|
| AUC <sub>inf</sub> (hr*ng/mL)  | 14,000 (62.6)     | 9,110 (60.4)      | -                   |
| AUC <sub>0-92</sub> (hr*ng/mL) | 14,200 (62.6)     | 9,210 (60.2)      | 151 (91.7, 250)     |
| C <sub>max</sub> (ng/mL)       | 82.7 (82.1)       | 26.8 (55.1)       | 261 (151, 452)      |
| T <sub>max</sub> (hours)       | 6.00 (4.00, 9.00) | 4.00 (4.00, 6.00) | -                   |
| t <sub>1/2</sub> (days)        | 12.6 (10.4, 15.3) | 13.1 (11.9, 15.0) | -                   |
| Plasma protein binding (%)     | 99.6 (0.194)      | 99.8 (0.145)      | -                   |

\*Pharmacokinetic parameters are presented to 3 significant figures as mean (SD) except T<sub>max</sub> and t<sub>1/2</sub> which are presented as median (Q1, Q3).  
 \*HI = Hepatic Impairment; HC = Healthy controls; GLSM = Geometric Least Squares Mean; CI = Confidence Interval  
 \*N=10 for AUC<sub>inf</sub>, AUC<sub>0-92</sub> and t<sub>1/2</sub>

**376 MODEL-INFORMED DOSE SELECTION FOR ISLATRAVIR/MK-8507 ORAL ONCE-WEEKLY PHASE 2B STUDY**

Bhargava Kandala<sup>1</sup>, Craig Fancourt<sup>1</sup>, Hari Krishna Ananthula<sup>1</sup>, Youfang Cao<sup>1</sup>, Pavan Vaddady<sup>1</sup>, Ernest Asante-Appiah<sup>1</sup>, Tracy L. Diamond<sup>1</sup>, Elizabeth G. Rhee<sup>1</sup>, Randolph P. Matthews<sup>1</sup>, Wendy Ankrom<sup>1</sup>, Ryan Vargo<sup>1</sup>

<sup>1</sup>Merck & Co, Inc, Kenilworth, NJ, USA

**Background:**

The novel 2-drug, once weekly (QW) oral combination of Islatravir (ISL) and MK-8507 is in development for the treatment of HIV-1, with the potential to decrease pill burden and dosing frequency. ISL is a first in class NRTTI that is being developed for treatment and prevention of HIV-1. Single doses of MK-8507, a novel NNRTI, achieved robust viral load declines for at least a week post-dose in treatment-naïve people living with HIV (PLWH). Dose selection was determined via modeling and simulation for an ISL+MK-8507 dose ranging Phase 2b study. [NCT04564547]

**Methods:**

Concentrations of ISL-triphosphate (ISL-TP), the intracellular active moiety, following QW administration of ISL were predicted using a population pharmacokinetic (PK) model. MK-8507 concentrations were also predicted using a population PK model. A Viral Dynamics Model (VDM) for ISL and

MK-8507 was used to predict efficacy for a range of QW doses of ISL (5 – 30 mg) and MK-8507 (50 – 400 mg). The VDM combines PK (drug exposures and the associated population variability), pharmacodynamic inhibitory effect (clinical  $IC_{50}$  of ISL and MK-8507 estimated from treatment-naïve monotherapy studies;  $IC_{50}$  fold reduction due to resistance-associated variants) and viral dynamics to predict trial outcome as measured by percent efficacy (% of participants with HIV-1 RNA below 50 copies/mL at 48 weeks). A real-world adherence model developed based on a claims database of PLWH receiving Abacavir/Dolutegravir/Lamivudine QD was applied.

#### Results:

A single dose of ISL 20 mg QW achieves ISL-TP trough concentrations comparable to steady state trough levels of ISL-TP for a dose of 0.75 mg QD, a dose shown to provide coverage for wild-type and common NRTI resistance associated variants including M184V. VDM simulations demonstrated that an oral 2-drug QW regimen containing ISL 20 mg in combination with MK-8507 100 mg, 200 mg or 400 mg doses provides 1) at least 90% efficacy and antiviral activity against the most common NRTI and NNRTI resistance-associated variants and 2) robust viral load suppression and efficacy in the event of a late or missed dose and real-world adherence patterns.

#### Conclusion:

This analysis supports selection of ISL 20 mg in combination with MK-8507 100 mg, 200 mg or 400 mg for further development as a QW regimen.

### 377 IN SILICO PREDICTION OF MONTHLY BICTEGRIVIR MICRONEEDLE ARRAY PATCHES

**Hannah Kinvig**<sup>1</sup>, Fazila S. Bunglawala<sup>1</sup>, Nicolas Cottura<sup>1</sup>, Maiara C. Montanha<sup>1</sup>, Andrew Lloyd<sup>1</sup>, Kurtis Moffatt<sup>2</sup>, Chunyang Zhang<sup>2</sup>, Ryan Donnelly<sup>2</sup>, Marco Siccardi<sup>1</sup>  
<sup>1</sup>University of Liverpool, Liverpool, UK, <sup>2</sup>Queen's University Belfast, Belfast, UK

#### Background:

Microneedle array patches (MAPs) comprise of multiple micron-scale needles that can provide painless administration of long-acting nanoformulated drug, producing effective drug plasma concentrations over extended periods of time. The current study used physiologically-based pharmacokinetic (PBPK) modelling to predict optimal dosing strategies of bictegravir (BIC) via MAP administration.

#### Methods:

A whole-body PBPK model was designed in Simbiology v.9.4 (MATLAB R2018a) and used to simulate 100 healthy individuals aged 18-60 years. Transdermal MAP administration was verified previously using cabotegravir and rilpivirine and was implemented into the BIC PBPK model. The BIC model was verified against reported clinical data for the oral administration of 5mg-100mg BIC once daily (QD). The PBPK model was assumed to be verified if the simulated values were within 0.8-1.55-fold of the reported clinical values and if the absolute average-fold error (AAFE) was below 1.55. The verified BIC model was used to simulate three once-monthly (QMT) MAP administrations following four weeks of 50mg BIC QD oral administration as oral lead in. Two dosing strategies were assessed, three MAPs with the same dose and one MAP with a higher loading dose followed by two MAPs with a lower maintenance dose. The protein adjusted (PA)- $IC_{50}$  of BIC (162 ng/ml) was considered as the minimum target plasma concentration. A range of MAP doses with varying release rates were simulated to determine the most efficient dosing strategy that achieved the target concentration.

#### Results:

The BIC PBPK model was successfully verified according to the criteria. MAP doses between 140-180 mg were simulated for the administration of three identical MAPs, with release rates between 0.0005-0.0025 h<sup>-1</sup> being assessed. The optimised dose and release rate from these simulations were then applied as the loading dose with a range of MAP doses between 90-130 mg being simulated for the maintenance dose. The simulated minimum concentration (C<sub>min</sub>) of BIC at the end of each MAP dosing interval for the optimised strategies are summarised in the table, including their estimated patch sizes.

#### Conclusion:

The PBPK model identified suitable dose and release rate strategies with practical patch sizes for QMT MAP administration of BIC. These simulations support the case for long-acting BIC MAPs and the data can inform strategies to address the technological challenges in the development of this alternative drug delivery system for antiretroviral therapy.

| Dose (mg)/Patch Size (cm <sup>2</sup> ) | Release Rate (h <sup>-1</sup> ) | BIC C <sub>min</sub> mean ± SD (ng/ml) |                |                 |
|---|---------------------------------|--|----------------|-----------------|
|   |                                 | Month 1                                | Month 2        | Month 3         |
| 150/36.7                                | 0.0015                          | 171.01 ± 67.71                         | 232.51 ± 92.01 | 254.41 ± 100.65 |
| 150/36.7 LD<br>100/24.5 MD              | 0.0015                          | 171.81 ± 89.1                          | 176.32 ± 91.37 | 177.85 ± 92.15  |

Patch size calculated based on 32.7 mg of drug per 8 cm<sup>2</sup> MAP, as previously described. C<sub>min</sub> mean ± SD calculated from 100 virtual healthy adults aged 18 – 60 years. Minimum target concentration of 162 ng/ml. LD – loading dose (month 1), MD – maintenance dose (month 2 & 3). BIC – bictegravir, SD – standard deviation.

### 378 PBPK MODELING OF DEXAMETHASONE IN PATIENTS WITH COVID-19 AND LIVER DYSFUNCTION

**Maiara C. Montanha**<sup>1</sup>, Nicolas Cottura<sup>1</sup>, Michael Booth<sup>1</sup>, Catherine E. Hodge<sup>1</sup>, Hannah Kinvig<sup>1</sup>, Fazila S. Bunglawala<sup>1</sup>, Andrew Lloyd<sup>1</sup>, Saye Khoo<sup>1</sup>, Marco Siccardi<sup>1</sup>  
<sup>1</sup>University of Liverpool, Liverpool, UK

**Background:** Patients with pre-existing multimorbidity and liver dysfunction (LD) are more likely to develop severe COVID-19 and have a higher risk of mortality. In severe COVID-19 patients who are mechanically ventilated or require supplemental oxygen, the administration of dexamethasone (DEX) may be life-saving, however the impact of LD on the pharmacokinetics (PK) of DEX is unknown. The aim of the study was to apply PBPK modelling to predict the effect of LD on the PK of DEX in the treatment of COVID-19.

**Methods:** A whole-body PBPK model was designed in Simbiology v. 9.6.0 (MATLAB R2019a) and used to simulate 100 adult individuals. First the model was qualified against reported clinical data for oral (PO) and intravenous (IV) DEX in healthy adults. Physiological changes and portal vein shunt were incorporated into the model to provide a mathematical description of LD that was classified by Child-Pugh (CP) scores A, B and C. The LD model was qualified against IV and PO reported clinical data for both propranolol (healthy adults and CP-A, -B and -C patients) and midazolam (healthy adult and cirrhosis patients). The model was assumed to be verified if the simulated values were within 2-fold of the reported clinical values and if the absolute average-fold error (AAFE) was below 2. The qualified model was then used to simulate the administration of DEX 6 mg (COVID-19 protocol) in patients with LD (CP-A, -B and -C) with and without shunting. The mean shunt index (%) considered in the model was 40 ± 18.

**Results:** The PBPK model was successfully qualified across DEX, midazolam and propranolol with an AUC<sub>0-24</sub> average fold of 1.1 and 0.95; AAFE value of 1.1 and 1.2 for healthy and LD individuals, respectively. When compared to healthy adults, the simulated systemic clearance of DEX decreased and the plasma concentrations increased in all patients with LD, as shown in Table 1. Moreover, a significant difference was observed between the AUC<sub>0-24</sub> of DEX PO when comparing no shunting and shunting in patients with CP-B and -C.

**Conclusion:** The increased exposure of DEX in different stages of LD was predicted through PBPK modelling, providing a rational framework to predict PK in complex clinical scenarios related to COVID-19. Although DEX exposure was predicted to be more than 2 times higher in CP-C individuals, no dose adjustments seem necessary in patients with LD considering DEX's low hepatic extraction, the low dose administered in the COVID-19 protocol and the therapeutic index of DEX.

**Table 1.** Simulated pharmacokinetic parameters of dexamethasone following oral and IV administration in Child-Pugh A, B and C patients with and without shunting.

| Parameters                    |                             | IV Dose      |              |              | PO Dose      |               |               |
|-------------------------------|-----------------------------|--------------|--------------|--------------|--------------|---------------|---------------|
|                               |                             | CP-A         | CP-B         | CP-C         | CP-A         | CP-B          | CP-C          |
| AUC <sub>0-24</sub> (ng.h/ml) | No Shunting                 | 566.9 (16.4) | 692.9 (15.2) | 833.6 (13.7) | 502 (18.2)   | 577.1 (14.8)  | 713.8 (14.7)  |
|                               | Ratio (No Shunting/Healthy) | 1.4          | 1.7          | 2.1          | 1.5          | 1.8           | 2.2           |
|                               | Shunting                    | 568 (14.5)   | 686.5 (13.2) | 827 (13.8)   | 506.8 (14.2) | 632.7 (16.2)* | 745.1 (14.6)* |
|                               | Ratio (Shunting/Healthy)    | 1.4          | 1.7          | 2            | 1.5          | 1.9           | 2.3           |
| CL (L/h)                      | No Shunting                 | 10.8 (17.7)  | 8.7 (16.6)   | 7 (15.2)     | 10.5 (18.4)  | 8.8 (15.5)    | 7.1 (15.4)    |
|                               | Ratio (No Shunting/Healthy) | 0.7          | 0.6          | 0.5          | 0.7          | 0.6           | 0.5           |
|                               | Shunting                    | 10.7 (16.1)  | 8.7 (13.9)   | 7.1 (15.6)   | 10.8 (14)    | 8.5 (16.2)    | 7.1 (14.4)    |
|                               | Ratio (Shunting/Healthy)    | 0.7          | 0.6          | 0.5          | 0.7          | 0.5           | 0.5           |

Data are presented as the mean (coefficient of variation, %). IV, intravenous; PO, oral. CP-A, CP-B and CP-C correspond to the Child-Pugh score. AUC<sub>0-24</sub> area under the plasma concentration-time curve over a dosing interval. CL, clearance. Statistical significance, \*p < 0.05.

### 379 IN VIVO EVALUATION OF LONG-ACTING BIODEGRADABLE EMTRICITABINE IMPLANTS

**Megan Neary**<sup>1</sup>, Joanne Sharp<sup>1</sup>, Paul Curley<sup>1</sup>, Henry Pertinez<sup>1</sup>, Helen Box<sup>1</sup>, Lee Tatham<sup>1</sup>, Danielle Brain<sup>1</sup>, Faye Hern<sup>1</sup>, Anika Shakil<sup>1</sup>, Chung Liu<sup>1</sup>, Caren Meyers<sup>2</sup>, Charles W. Flexner<sup>2</sup>, Steve Rannard<sup>1</sup>, Andrew Owen<sup>1</sup>

<sup>1</sup>University of Liverpool, Liverpool, UK, <sup>2</sup>The Johns Hopkins University, Baltimore, MD, USA

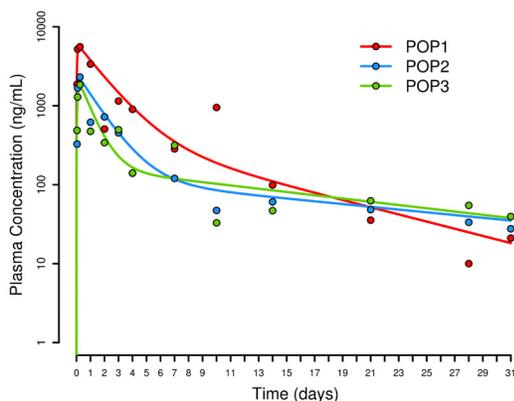
**Background:** Long-acting (LA) antiretroviral interventions hold promise to revolutionise HIV therapy and prevention and mitigate key concerns regarding adherence to oral medications. The current study investigated a biodegradable

subcutaneous implant derived from a polymer formed entirely from an emtricitabine (FTC) prodrug (POP implant).

**Methods:** For in vitro studies, POP implants were incubated in 1 mL of phosphate buffered saline containing human liver microsomes at 37 °C/ 125 rpm for 72 hours. Every 24 hours, 500 µL samples were taken and replaced with 500 µL of fresh buffer to maintain sink conditions. For in vivo evaluations, two POP implants (2mm x 15mm each) were inserted subcutaneously into the scapular region of male Wistar rats under anaesthetic with 3% isoflurane. Plasma samples were obtained 1-6 hours and 1-31 days post implantation. FTC concentrations were quantified using a validated LC-MS/MS assay.

**Results:** Eleven candidates were screened in vitro and three were selected for animal studies with in vitro release rates of 145, 59 and 7 µg/day for POP1, POP2 and POP3, respectively. In vitro release rate was determined from the linear phase of the profile. The plasma pharmacokinetics of the three implants are shown in Figure 1, with a  $C_{max}$  of 5581, 2306 and 1847 ng/mL, AUC<sub>0-tlast</sub> of 14,614, 4644, and 4616 ng.days/mL and  $C_{min}$  of 10, 27 and 32 ng/mL for POP1, POP2 and POP3, respectively. Plasma concentration profiles following implantation could be empirically described by a 2-compartment model with first order input, reflecting the drug release and flip-flop kinetics rather than the intrinsic pharmacokinetic disposition of FTC seen previously for intravenous administration. Apparent clearance was 0.7, 1.6 and 2.0 L/h/kg with final phase half-life of 6.6, 17.3, and 14.6 days for POP1, POP2 and POP3 respectively. In vitro-in vivo correlation for AUC<sub>0-tlast</sub> and  $C_{max}$  revealed R<sup>2</sup> values of 0.87 and 0.93, and an inverse correlation with  $C_{min}$  (R<sup>2</sup> = 0.98), demonstrating the relationship between in vitro release and in vivo exposure.

**Conclusion:** These data support LA drug delivery from a biodegradable polymer implant manufactured exclusively from an FTC prodrug for over 31-days. The relevance of human target exposures in rat studies are unclear, but concentrations remained above the reported FTC EC<sub>90</sub> for 14, 10 and 7 days for POP1, POP2 and POP3, respectively. Ongoing studies seek to optimise exposures that can be achieved for FTC and POP implants manufactured from other antiretroviral drugs.



### 380 PHARMACOGENOMIC TESTING PROVIDES INSIGHT AND ENHANCES MEDICATION MANAGEMENT IN PLWHIV

John D. Zeuli<sup>1</sup>, Christina G. Rivera<sup>1</sup>, Mary J. Kasten<sup>1</sup>, Maryam Mahmood<sup>1</sup>, Stacey A. Rizza<sup>1</sup>, Zelalem Temesgen<sup>1</sup>, John W. Wilson<sup>1</sup>, Jessica A. Wright<sup>1</sup>, Nathan W. Cummins<sup>1</sup>

<sup>1</sup>Mayo Clinic, Rochester, MN, USA

**Background:** Pharmacogenomics is the area of individualized medicine focused on genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and drug targets that explain inter-individual variation in drug efficacy and toxicity. Single gene assessment of HLA-B\*57:01 prior to abacavir use is well-established in the care of PLWHIV. However, pharmacogenomic panel testing (assessing multiple genes rather than a single gene of interest) has become economically feasible and scalable to larger populations, providing more detailed information to enhance safe and effective medication therapy for PLWHIV. Clinical data on the utility of pharmacogenomic panels in PLWHIV is not available. Our study aimed to assess the impact of pharmacogenomic panel testing in PLWHIV.

**Methods:** One hundred PLWHIV were provided a comprehensive pharmacogenomic panel during routine care visits within the HIV specialty clinic of a large academic medical center. The panel determined the presence

of specific genetic variants that could predict response or toxicity to commonly prescribed antiretroviral therapy (ART) and non-ART medications. An HIV specialty pharmacist reviewed the results with patients and the care team. The pharmacist: (1) recommended clinically actionable interventions based on the patients current drug therapy, (2) assessed for genetic explanations for prior medication failures, adverse effects, or intolerances, and (3) advised on potential future clinically actionable care interventions based on individual genetic phenotypes.

**Results:** Ninety-six patients completed panel testing with 656 clinically relevant pharmacogenomic results (109 major, 547 mild-moderate). Eighty-nine patients completed follow-up visits with the HIV pharmacist, and 47 (53%) were provided new clinical recommendations based on their current medication profile, the majority related to monitoring for efficacy or toxicity. Clinical recommendations were associated with a major genetic finding or determined to be of significant clinical importance in twenty patients (22%). Panel results offered potential explanations of prior ART intolerance in 28% of patients and explanation for ART inefficacy in 1 patient. Genetic explanation for non-ART toxicity was seen in 20% of patients, with genetic contributors to inefficacy of non-ART therapy identified in 37% of patients.

**Conclusion:** Preliminary data in a small cohort of PLWHIV demonstrates benefit of routine pharmacogenomic panel testing.

Table: Clinical findings by patient after pharmacogenomic panel result review

| n=89   | ART      |        | Other medications |         |
|--|----------|--------|-------------------|---------|
|  | Mild-Mod | Major  | Mild-Mod          | Major   |
| <b>Clinical Recommendations-Current Medication Profile</b> |          |        |                   |         |
| Total  | 35 (39%) |        | 47 (53%)          |         |
| Adjustment   | 0        | 0      | 6                 | 5       |
| Monitoring   | 27       | 6      | 25                | 7       |
| Other  | 2        | 0      | 14                | 2       |
| <b>Historic medication adverse effects identified</b>      |          |        |                   |         |
|  | 20 (22%) | 5 (6%) | 10 (11%)          | 9 (10%) |
| <b>Historic medication efficacy issues identified</b>      |          |        |                   |         |
|  | 0        | 1 (1%) | 25 (28%)          | 8 (9%)  |

### 381 A NOVEL COVID-19 CURE STRATEGY: HIJACKING SARS-CoV-2 RNA-DEPENDENT RNA POLYMERASE

Serhat Gumrukcu<sup>1</sup>, Tung X. Nguyen<sup>1</sup>, Michael D. Bobardt<sup>2</sup>, Philippe Gallyay<sup>2</sup>  
<sup>1</sup>Seraph Research Institute, Los Angeles, CA, USA, <sup>2</sup>The Scripps Research Institute, La Jolla, CA, USA

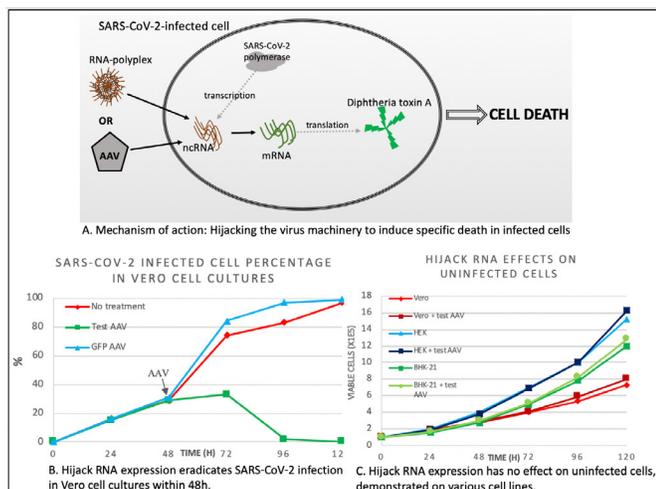
**Background:** SARS-CoV-2 is a single-stranded positive-sense RNA virus that utilizes a negative-sense subgenomic (sg)RNA intermediates for viral protein synthesis. We developed a synthetic RNA ("hijack RNA") that is designed to be recognized by SARS-CoV-2 RNA-dependent RNA polymerase (RdRp). Upon recognition, hijack RNA is transcribed into diphtheria toxin fragment A (DT-A), to induce death specifically in infected cells, which could be a potential treatment(Fig 1A).

**Methods:** Adeno-associated virus (AAV) was packaged with a novel vector expressing our SARS-CoV-2 hijack RNA, which contains reverse complementary strand of DT-A cDNA, flanked between secondary structures of SARS-CoV-2 sgRNA. Vero, Calu3 and HepG2 cells that were uninfected or infected with SARS-CoV-2 USA-WA1/2020 strain at 0.1 MOI, were transduced with test or GFP (control) AAVs. Uninfected jurkat, HEK and BHK-21 cells were also transduced with test AAV to assess off-target effects of hijack RNA. Cell death and viability were evaluated daily by FACS and automated cell count. The same experiments were repeated on SARS-CoV-2 RdRp expressing Vero and HepG2 cell lines to validate hijack RNA's specificity to RdRp. SCID mice were subcutaneously injected with HepG2-SARS-CoV-2-FLuc cells to establish an in vivo bioluminescent SARS-CoV-2 infection model. Mice were treated with test AAV two weeks after xenotransplantation. Infected cell killing was monitored by in vivo imaging on IVIS.

**Results:** SARS-CoV-2 infection was eradicated from Vero, Calu3 and HepG2 cultures within 48h after test AAV transduction, confirmed by FACS analysis, cell proliferation assays and the absence of CPE in cell imagery(Fig 1B). Test AAV, or presence of hijack RNA, had no effect on uninfected cells(Fig 1C). Similar results were observed in RdRp expressing cell lines, confirming the hypothesized mechanism of action and the hijack RNA's dependence on SARS-CoV-2 RdRp. Results of ongoing in vivo studies will be presented.

**Conclusion:** An mRNA delivered or expressed in trans to engage with SARS-CoV-2 RdRp successfully hijacked the virus machinery to induce rapid death in infected cells but not in uninfected cells, resulting in total eradication of the

virus within 48h. Hijack RNA's transcription into the kill molecule DT-A was dependent on viral RdRp, confirming the specificity this potential treatment. This novel approach could be used to develop an effective treatment, potentially in the form of an AAV or an aerosolized RNA drug to rapidly eradicate COVID-19 infection.



### 382 NOVEL ENTRY INHIBITORS AGAINST SARS-CoV-2 BASED ON INTERFACE OF SPIKE RBD

Arpan Acharya<sup>1</sup>, Kabita Pandey<sup>1</sup>, Michellie Thurman<sup>1</sup>, Elizabeth Klug<sup>1</sup>, Kamal Singh<sup>2</sup>, Siddappa N. Byrareddy<sup>1</sup>

<sup>1</sup>University of Nebraska Medical Center, Omaha, NE, USA, <sup>2</sup>University of Missouri, Columbia, MO, USA

**Background:** Background: Since the outbreak of COVID-19, globally, more than 63 million people have been infected and 1.46 million people succumbed to death, and the number is still growing. It is well-established that attachment of spike glycoprotein of SARS-CoV-2 with ACE-2 is crucial for initiating infection. While a vaccine is awaited, alternate strategies can be adopted for blocking viral entry to host cells. Herein, we report two lead compounds that block the attachment of spike with ACE2 using lung epithelial cells.

**Methods:** Methods: To identify the lead compounds, we conducted virtual screening of ~3 million compounds that had potential to bind a site at ACE2/ Spike interface (PDB file 6MOJ) using 'Glide' program of Schrödinger Suite. Then the combination of visual inspection and redocking with AutoDock Vina (to determine binding energy) was used to select 5 potential inhibitors of ACE2/ Spike interaction. These five compounds were then tested for their inhibitory activity in virological and biophysical assays. The inhibitory activity of these five compounds was measured using Vero-STAT1 knockout cells and a human bronchial epithelial cell line (UNCNTT).

**Results:** Results: Of the five, two compounds, MU-UNMC-1 and MU-UNMC-2 with binding energy of -6.9kcal/mol and -7.8kcal/mol respectively, showed antiviral activity in two cell lines. In Vero-STAT1 cells, MU-UNMC-1 had IC<sub>50</sub> of 5.35μM and 2.94μM, whereas MU-UNMC-2 had IC<sub>50</sub> of 1.63μM and 0.54μM, after 24 and 48 hrs post infection (hpi), respectively. In UNCNTT cells, both compounds had significantly better efficacy. MU-UNMC-1 had an IC<sub>50</sub> of 0.67μM and 1.16μM and at 24 and 48 hpi, respectively. MU-UNMC-2 had IC<sub>50</sub> of 1.72μM and 0.89μM after 24 and 48 hpi, respectively. In Vero-STAT1 cells, the selectivity index (SI) (defined as CC50/IC<sub>50</sub>) of the compounds was 2.11(MU-UNMC-1) and 13.22(MU-UNMC-2), whereas in UNCNTT cells, the SI of the compounds was 9.27(MU-UNMC-1) and 4.15(MU-UNMC-2).

**Conclusion:** Conclusion: We report the identification of two lead compounds (MU-UNMC-1 and MU-UNMC-2) that block the entry of SARS-CoV-2 in sub-micromolar concentration in biologically relevant human bronchial epithelial cells. Further, using structure-based similarity searches, we identified three additional chemotypes of these two compounds. These chemotypes of MU-UNMC-3, MU-UNMC-4 and MU-UNMC-5 showed ~2-fold better binding affinity with ACE2/Spike complex. These compounds are under investigation for their inhibitory effect in virological and biophysical assays.

### 383 RATIONALLY DESIGNED ACE2-DERIVED PEPTIDES INHIBIT SARS-CoV-2

Ross C. Larue<sup>1</sup>, Enming Xing<sup>1</sup>, Adam D. Kenney<sup>1</sup>, Yuexiu Zhang<sup>1</sup>, Jasmine Tuazon<sup>1</sup>, Jianrong Li<sup>1</sup>, Jacob Yount<sup>1</sup>, Pui-Kai Li<sup>1</sup>, Amit Sharma<sup>1</sup>

<sup>1</sup>The Ohio State University, Columbus, OH, USA

**Background:** Severe acute respiratory syndrome coronavirus (SARS-CoV)-2 is a novel and highly pathogenic coronavirus and is the causative agent of the coronavirus disease 2019 (COVID-19). The high morbidity and mortality associated with COVID-19 and the lack of an approved drug or vaccine for SARS-CoV-2 underscores the urgent need for developing effective antiviral therapies. Therapeutics that target essential viral proteins are effective at controlling virus replication and spread. Coronavirus Spike glycoproteins mediate viral entry and fusion with the host cell, and thus, are essential for viral replication. To enter host cells, the Spike proteins of SARS-CoV-2 and related coronavirus, SARS-CoV, bind the host angiotensin-converting enzyme 2 (ACE2) receptor through their receptor binding domains (RBDs).

**Methods:** We performed comparative analyses of the SARS-CoV and SARS-CoV-2 RBD-ACE2 interaction interfaces to rationally design a panel of Spike-targeting ACE2-derived peptides (SAPs). Antiviral potencies of SAPs were evaluated against lentiviral vectors pseudotyped with SARS-CoV-2 or SARS-CoV Spike glycoproteins. Affinity precipitation assays were employed to determine the binding affinities of SAPs to recombinant SARS-CoV-2 RBD. Antiviral potential of selected SAPs was also validated against two pathogenic human coronaviruses, SARS-CoV-2 and HCoV-NL63, both of which use ACE2 as entry receptors.

**Results:** We designed six SAPs – four derived from α1, one derived from α3, and one derived from α11 helix of ACE2. Three of the six SAPs inhibited SARS-CoV-2 and SARS-CoV Spike-mediated virus infection with IC<sub>50</sub> values in the low millimolar range. The in vitro SAP-RBD binding affinities tracked closely with their antiviral IC<sub>50</sub> values. Importantly, two SAPs inhibited SARS-CoV-2 and HCoV-NL63 infections. Results from the infection experiments and modeling of the peptides with RBD identified a six amino acid (Glu37-Gln42) ACE2 motif that is important for SARS-CoV-2 inhibition.

**Conclusion:** We rationally designed a panel of ACE2-derived peptides based on the RBD-ACE2 binding interfaces of SARS-CoV-2 and SARS-CoV. We identified two peptides that inhibited infection with genuine SARS-CoV-2. Our work demonstrates the feasibility of inhibiting SARS-CoV-2 with peptide-based inhibitors. These findings will allow for the successful development of engineered peptides and peptidomimetic-based compounds for the treatment of COVID-19.

### 384 RNHC INHIBITS SARS-CoV-2 IN VITRO BUT IS MUTAGENIC IN MAMMALIAN CELLS

Shuntai Zhou<sup>1</sup>, Collin Hill<sup>1</sup>, Sanjay Sarkar<sup>1</sup>, Victor Tse<sup>1</sup>, Timothy Sheahan<sup>1</sup>, Ralph Baric<sup>1</sup>, Mark Heise<sup>1</sup>, Ronald Swanstrom<sup>1</sup>

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

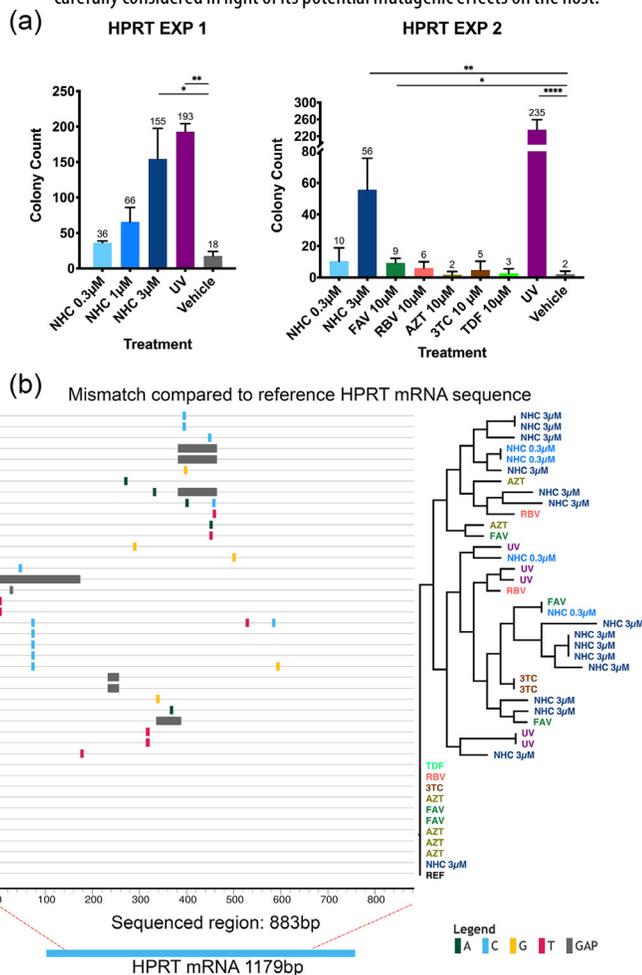
**Background:** We previously showed that β-D-N4-hydroxycytidine (rNHC) and its orally bioavailable prodrug, molnupiravir, acts as a broad-spectrum antiviral against coronaviruses in vitro and in vivo through lethal mutagenesis. Molnupiravir is currently in clinical trials for the treatment of SARS-CoV-2 infection. However, there are concerns that rNHC could be metabolized to dNHC and cause mutations in host cells. We examined the in vitro antiviral and mammalian cell mutagenic activity of three different nucleoside/base analogs, rNHC, favipiravir, and ribavirin, on SARS-CoV-2. We further examined the in vitro genotoxicity of a panel of antiviral nucleotide/nucleoside analogs, including rNHC, using a modified HPRT gene mutation assay.

**Methods:** A549-hACE2 cells were infected with SARS-CoV-2 in the presence of nucleoside analogs. After 48 hours, the supernatants were collected and viral RNA was extracted. We constructed multiplexed-Primer ID libraries from viral RNA and sequenced them using MiSeq. HPRT knockout assays were performed using CHO-K1 cells treated with a panel of nucleotide/nucleoside analogs for 32 days. After 6-thioguanine selection, resistant cell colonies were counted as a measure of HPRT knockout mutations in host cells, and HPRT mRNA was sequenced from selected colonies.

**Results:** rNHC showed dose-dependent antiviral and mutagenic effects against SARS-CoV-2 in vitro. In the 10 μM group, we found 7-fold and 14-fold increases in the overall substitution rate and the C to U mutation rate, respectively. The HPRT assay showed an rNHC dose-dependent increase in the number of resistant colonies with HPRT gene mutations. Other analogs showed no significant increase in the number of 6-thioG resistant colonies except for a slight increase

with favipiravir (Fig 1a). Most colonies had missense substitutions or frame-shift deletions within HPRT mRNA, with most being distinct.

**Conclusion:** rNHC showed a dose-dependent inhibition and mutagenic effect of SARS-CoV-2 in vitro. However, rNHC would be expected to be metabolized into the deoxynucleotide pool (by host RNR), resulting in DNA mutation of dividing mammalian cells. We demonstrated such mutagenic potential in a simple mammalian cell detection scheme. Molnupiravir has considerable potential as an orally bioavailable direct acting antiviral against SARS-CoV2 early in infection, especially in high risk patients. However, clinical use should be carefully considered in light of its potential mutagenic effects on the host.



**Fig. 1.** HPRT assay to detect genotoxicity of β-D-N4-hydroxycytidine (NHC), ribavirin (RBV), favipiravir (FAV), zidovudine (AZT), lamivudine (3TC) and tenofovir (TDF) in CHO-K1 cells in vitro. (a) HPRT mutation colony counts in two separate HPRT experiments. In the HPRT EXP2, an additional round of cleansing for spontaneous HPRT mutation was conducted to limit the background mutation. Each compound/dose group had 3 replicates. Average numbers of colonies are shown on the top of each bar. (b) The highlighter plot of the HPRT mutation colony sequencing from the second experiment. HPRT colonies were scraped from the cell culture dishes and transferred into 24-well tissue culture plates in complete growth medium with 30µM 6-TG for 4 days. Cells in each well were collected and total RNA were extracted. We amplified the HPRT mRNA using one-step RT-PCR and sequenced the PCR products with Sanger sequencing. The total sequenced region were 883 bases of the total 1179-base HPRT mRNA (XM\_007643626.2), with regions on each end of the mRNA not covered by sequencing. Each colony sequence was compared with the reference mRNA sequence. A total of 42 colonies were sequenced and 32 of them had missense substitutions or frame-shifts from deletions. Most of the mutations are different, while a few colonies contained the identical mutation. Notably, we found 3 colonies in one NHC 3µM replicate and 2 colonies from another NHC 3µM replicate had identical mutations.

**385 ANTI-SARS-CoV-2 MULTI-DOMAIN DARPIN<sup>®</sup> MOLECULES AS HIGHLY POTENT THERAPEUTICS**

**Marcel Walsler<sup>1</sup>**, Sylvia Rothenberger<sup>2</sup>, Daniel L. Hurdiss<sup>3</sup>, Anja Schlegel<sup>1</sup>, Valerie Calabro<sup>1</sup>, Keith M. Dawson<sup>1</sup>, Micha A. Häuptle<sup>1</sup>, Sarah Taplin<sup>4</sup>, Christof Zitt<sup>1</sup>, Leon De Waal<sup>5</sup>, Frank J. Van Kuppeveld<sup>3</sup>, Olivier Engler<sup>2</sup>, Berend-Jan Bosch<sup>3</sup>, Michael T. Stumpff<sup>1</sup>, Patrick Amstutz<sup>1</sup>

<sup>1</sup>Molecular Partners AG, Zürich-Schlieren, Switzerland, <sup>2</sup>Spiez Laboratory, Spiez, Switzerland, <sup>3</sup>Utrecht University, Utrecht, Netherlands, <sup>4</sup>Integrated Biologix, Basel, Switzerland, <sup>5</sup>Viroclinics Xplore, Schaijk, Netherlands

**Background:** Globally accessible preventive and therapeutic drugs against SARS-CoV-2 are urgently needed. Here, we report the generation and

characterization of the first anti-SARS-CoV-2 DARPIN<sup>®</sup> molecules with therapeutic potential. DARPIN<sup>®</sup> molecules are an emerging class of novel therapeutics based on naturally occurring ankyrin repeat motifs which can be rapidly produced in bacteria in large quantities.

**Methods:** From a naïve library of 1012 DARPIN molecules 380 molecules were selected to target the SARS-CoV-2 spike protein. Extensive biophysical and biochemical characterization, pseudovirus and infectious virus neutralization assays as well as cryo-EM analysis, resulted in 11 highly distinct single domain DARPIN molecules which were used for the assembly of highly potent multi-domain DARPIN molecules. The protective efficacy of multi-domain DARPIN molecules was studied in COVID-19 hamster models.

**Results:** From the 11 single domain DARPIN molecules a range of multi-domain DARPIN molecules were assembled which were grouped into multi-paratopic DARPIN molecules neutralizing the receptor binding domain (RBD) and multi-mode DARPIN molecules targeting simultaneously the RBD, the S1 N-terminal-domain (NTD) and/or the S2 domain. Multi-domain DARPIN molecules binding three spike protein domains simultaneously demonstrated increased binding affinity, virus neutralization potency and the potential to prevent viral escape via mutations. Cryo-EM analysis further supported the structural understanding of the multi-domain DARPIN molecules and molecular modelling proved that simultaneous binding of individual DARPIN domains to various spike protein domains is feasible. Two additional DARPIN domains binding human serum albumin were incorporated in the DARPIN molecules, conferring an expected half-life of about 3 weeks in humans. A multi-paratopic RBD-neutralizing DARPIN molecule and a multi-mode DARPIN molecule were found to potentially block SARS-CoV-2 infection with IC<sub>50</sub> values in the single-digit ng/mL range. Multi-paratopic DARPIN molecules proved prophylactic and therapeutic efficacy in hamster SARS-CoV-2 infection models.

**Conclusion:** The anti-SARS-CoV-2 multi-domain DARPIN molecule, ensovibep or MPO420, which entered clinical phase I in November 2020, displayed very high antiviral potency, rapid and high production capacity due to bacterial fermentation and demonstrated prophylactic and therapeutic activity in hamster SARS-CoV-2 infection models.

**386 IDENTIFICATION OF REPURPOSING DRUGS AGAINST SARS-CoV-2 USING HUMAN LUNG TISSUES**

**Judith Grau-Expósito<sup>1</sup>**, David Perea<sup>1</sup>, Nuria Massana<sup>1</sup>, Marina Suppi<sup>1</sup>, Joel Rosado<sup>2</sup>, Javier García-Pérez<sup>3</sup>, José Alcamí<sup>3</sup>, Anna Serrano<sup>4</sup>, Vicenç Falcó<sup>2</sup>, Meritxell Genescà<sup>1</sup>, Maria José Buzón<sup>1</sup>

<sup>1</sup>Vall d'Hebron Research Institute, Barcelona, Spain, <sup>2</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, <sup>3</sup>Institute of Salud Carlos III, Majadahonda, Spain, <sup>4</sup>Hospital Clinic of Barcelona, Barcelona, Spain

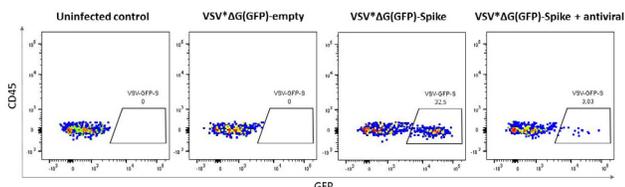
**Background:** No effective drugs against SARS-CoV-2 infection are available. Screening of therapeutic candidates is primarily performed using immortalized cell lines. However, primary cell targets might show intrinsic differences in the expression profile of relevant host proteins, required for viral replication that could significantly affect the activity and potency of antivirals. Thus, the development of more physiological models for antiviral drug screening are urgently needed.

**Methods:** Lung tissue was obtained from routinely thoracic surgical resections and was immediately digested before experiment set up. Cell populations and expression of ACE2 were characterized by FACS, and cell targets for SARS-CoV-2 were identified using a VSV\*ΔG(GFP)-S pseudotyped virus. 39 repurposing drugs previously identified by in silico models as potential viral entry inhibitors were tested using a VSV\*ΔG(Luc)-S virus. Cytotoxic concentration (CC50) and inhibitory concentration (IC50) values were calculated using a non-linear regression dose-response curve and were compared to drug activity in VeroE6 cells.

**Results:** Alveolar type II (AT-II) cells, the main cell target for SARS-CoV-2 infection in lungs, were identified within a fraction of cells characterized by CD45-, CD31-, EpCAM+ and HLA-DR+, (~0.01-0.5% of viable cells). Using a VSV\*ΔG(GFP)-S virus we showed that viral entry was occurring in cells compatible with an AT-II phenotype, and infection was efficiently blocked with an anti-ACE2 antibody (Figure 1). Despite low and variable numbers of AT-II targets, antiviral assays using VSV\*ΔG(Luc)-S were highly sensitive and reproducible (CV of 17%). Compared with VeroE6 cells, IC<sub>50</sub> values trended to be higher in tissues. Moreover, we found that 12.8% of the tested compounds had discordant results, where 10.25% of the drugs showed some antiviral effect in lung cell suspensions but no activity in VeroE6 and 3.9% showed only antiviral

effect in VeroE6. Modulation of ACE2 expression by some of these compounds was also highly discordant between the cell line and lung tissue. Cepharantine ( $IC_{50}=6\mu M$ ,  $CC50=14\mu M$ ) and Ergoloid ( $IC_{50}=4.3\mu M$ ,  $CC50=24\mu M$ ) were identified as the most active entry inhibitors in lung cell suspension.

**Conclusion:** The use of lung tissue for the screening of antiviral compounds represents a valid physiological and relevant model, which evidences intrinsic discrepancies with cell lines. Importantly, we identified repurposing drugs against SARS-CoV-2 with potential for clinical testing.



**Figure 1.** Lung cell suspensions were infected with VSV\*ΔG(GFP)-S pseudotyped virus. GFP was measured at 24h by flow cytometry in live CD45<sup>+</sup>, CD31<sup>+</sup>, EpCAM<sup>+</sup> and HLA-DR<sup>+</sup> cells. An uninfected sample, a VSV\*ΔG(GFP)-empty (residual VSV\*ΔG(GFP) in viral preparation), and a VSV\*ΔG(GFP)-Spike treated with an antiviral is shown.

### 387 THE 3CLpro INHIBITOR ALG-097111 POTENTLY INHIBITS SARS-CoV-2 REPLICATION IN HAMSTERS

**Koen Vanduyck**<sup>1</sup>, Rana Abdelnabi<sup>2</sup>, Kusum Gupta<sup>3</sup>, Dirk Jochmans<sup>2</sup>, Dinah Misner<sup>3</sup>, Jerome Deval<sup>3</sup>, Dorothee Bardiote<sup>4</sup>, Leonid Beigelman<sup>3</sup>, Lawrence M. Blatt<sup>3</sup>, Sandro Boland<sup>4</sup>, Patrick Chaltin<sup>5</sup>, Arnaud Marchand<sup>4</sup>, Pierre Raboisson<sup>1</sup>, Julian A. Symons<sup>3</sup>, Johan Neyts<sup>2</sup>

<sup>1</sup>Aligos Belgium BV, Leuven, Belgium, <sup>2</sup>Rega Institute for Medical Research, Leuven, Belgium, <sup>3</sup>Aligos Therapeutics, Inc., South San Francisco, USA, <sup>4</sup>CISTIM Leuven vzw, Leuven, Belgium, <sup>5</sup>Centre for Drug Design and Discovery, Leuven, Belgium

**Background:** There is an urgent need for potent drugs for the treatment or prevention of SARS-CoV-2 infections. Inhibition of viral proteases has been proven a successful therapeutic strategy for infections with HIV and HCV. Most reported inhibitors of the SARS-CoV-2 3-chymotrypsin-like (3CL) cysteine protease also target cathepsin L; the latter is involved in the SARS-CoV-2 entry process. We aim to develop potent and selective 3CL protease inhibitors devoid of cathepsin L inhibition.

**Methods:** Structure based optimization and biochemical profiling, resulted in ALG-097111, a potent and selective SARS-CoV-2 3CL protease inhibitor. ALG-097111 was profiled in vitro in SARS-CoV-2 and CoV-OC43 cellular assays. In vitro microsomal stability and in vivo PK evaluation in rodents, in presence of the CYP-inhibitor ritonavir, was followed by the evaluation of ALG-097111 in a SARS-CoV-2 infection model in hamsters.

**Results:** ALG-097111 exhibits potent SARS-CoV-2 3CLpro activity ( $IC_{50} = 0.007\mu M$ ) with no associated cathepsin L inhibition ( $IC_{50} > 10\mu M$ ). This selectivity extended to other human proteases, displaying less than 50% inhibition at  $10\mu M$ , as well as receptor and kinase panels. While ALG-097111 is stable in human and dog microsomes ( $t_{1/2} = >60$  min) and hepatocytes ( $t_{1/2} = >360$  min), ALG-097111 showed lower stability in hamsters specifically ( $t_{1/2} = 15$  min). Addition of ritonavir to the hamster microsome assay increased the in vitro half-life ( $t_{1/2} = >60$  min). When administered subcutaneously with oral co-dosing of ritonavir, ALG-097111 shows high plasma and lung exposures. Dosing hamsters with ALG-097111, followed by intranasal SARS-CoV-2 infection led to a significant reduction of infectious virus titers by  $3.7\log_{10}$  (TCID50/mg) and viral RNA by  $3.5\log_{10}$  (RNA copies/mg) in the lungs as compared to the vehicle group. In the same experiment, the nucleoside analogue Molnupiravir (EIDD-2801), used as a reference inhibitor, reduced infectious virus titers by  $4.1\log_{10}$  (TCID50/mg) and viral RNA load by  $2.0\log_{10}$  (RNA copies/mg).

**Conclusion:** We demonstrate that ALG-097111, a potent and selective inhibitor of the SARS-CoV-2 3CL protease that is devoid of any cathepsin L activity, reduces infectious virus titers in the lungs of SARS-CoV-2 infected hamsters to (almost) the detection limit. This validates the 3CL protease as an excellent target for the treatment of SARS-CoV-2 infections.

388

### A SARS-CoV-2-NEUTRALIZING ACE2 DECOY SHOWS HIGH AFFINITY FOR N501Y AND L452R VARIANTS

**Shiho Tanaka**<sup>1</sup>, Anders Olson<sup>1</sup>, Gard Nelson<sup>1</sup>, Oleksandr Buzko<sup>1</sup>, Wendy Higashide<sup>1</sup>, Annie Shin<sup>1</sup>, Marcos Gonzalez<sup>1</sup>, Justin Taft<sup>2</sup>, Roosheel Patel<sup>2</sup>, Sofija Buta<sup>2</sup>, Dusan Bogunovic<sup>2</sup>, Patricia R. Spilman<sup>1</sup>, Kayvan Niazi<sup>1</sup>, Shahrooz Rabizadeh<sup>1</sup>, Patrick Soon-Shiong<sup>1</sup>

<sup>1</sup>ImmunityBio, Inc, Culver City, CA, USA, <sup>2</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA

**Background:** SARS-CoV-2 infects the host by binding of its spike receptor binding domain (S RBD) to angiotensin converting enzyme 2 (ACE2) on the surface of cells in the respiratory tract and gut; thus therapeutics that prevent this interaction are of interest because they have the potential to inhibit propagation of infection. A recombinant 'ACE2 Decoy' that competitively binds S RBD and neutralizes SARS-CoV-2 infection represents such a therapeutic approach. The impact of S RBD mutations found in the rapidly spreading UK, South African, and California SARS-CoV-2 variants on ACE2 Decoy affinity is an important factor in design. Here, we identified a high-affinity SARS-CoV-2-neutralizing ACE2 Decoy that maintains its high affinity against RBD with mutations found in emerging variants.

**Methods:** We used Molecular Dynamic (MD) simulation of S RBD-ACE2 interactions to predict ACE2 residues that if mutated, might increase affinity for S RBD and thus successfully compete with endogenous ACE2 for binding. Recombinant ACE2-IgG1Fc and -IgAfc fusion proteins expressing mutations predicted to increase S RBD binding affinity were produced, purified, and screened for binding affinities against wild type S RBD and S RBD expressing E484K, K417N, N501Y, or L452R alone and in combinations of: K417N/N501Y; E484K/N501Y; K417N/E484K; and K417N/E484K/N501Y (found in the South African variant). The ability of the Decoy with the highest affinity to neutralize SARS-CoV-2 infection was determined by a live virus assay using Vero E6 cells. An additional mutation (H374N) to inhibit enzymatic activity of ACE2 was added to the Decoy with the highest affinity from mutation screening.

**Results:** Eleven of the ACE2 mutations predicted to increase affinity for S RBD were tested, revealing the ACE2 Decoy with T27Y and H34A mutations to have the highest S RBD affinity and the ability to neutralize SARS-CoV-2 infection of cells. Both the ACE2 wild type (WT)-IgG1Fc and the ACE2(T27Y/H34A/H374N)-IgG1Fc Decoys showed enhanced binding affinity for S RBD with either N501Y and L452R mutations alone. Interestingly, the South African variant K417N mutation alone decreased affinity, but not in combination with the N501Y mutation.

**Conclusion:** The potential efficacy of the ACE2 (T27Y/H34A/H374N)-IgG1Fc Decoy is not decreased by the UK, South African, or California variant mutations and will undergo testing in animal models likely by expression using a human adenovirus (hAd5) construct to enhance stability.

389

### TARGETING THE RECEPTOR AXL BY BEMCENTINIB PREVENTS SARS-CoV-2 INFECTION

**Dana Bohan**<sup>1</sup>, Hanora Van Ert<sup>1</sup>, Sushil Dhakal<sup>2</sup>, Natalie Ruggio<sup>1</sup>, Kai Rogers<sup>1</sup>, Tomasz Stokowy<sup>2</sup>, Gro Gausdal<sup>3</sup>, Akil Jackson<sup>4</sup>, Hani Gabra<sup>4</sup>, David R. Micklem<sup>3</sup>, James Lorens<sup>2</sup>, Wendy Maury<sup>1</sup>

<sup>1</sup>University of Iowa, Iowa City, IA, USA, <sup>2</sup>University of Bergen, Bergen, Norway, <sup>3</sup>BerGenBio ASA, Bergen, Norway, <sup>4</sup>BerGenBio Ltd, Oxford, UK

**Background:** SARS-CoV-2 enters host cells via an interaction between viral spike protein and cellular ACE2. However, in common with other enveloped viruses, apoptotic mimicry may also assist cell entry: phosphatidylserine (PS) exposed on the viral envelope interacts with cellular PS receptors leading to efferocytosis. The PS receptor, GAS6 bound to AXL, has also been shown to suppress type I interferon (IFN) responses. AXL is the predominant cellular PS receptor expressed on airway-derived cell lines. We hypothesized that the clinical-stage, AXL kinase-specific inhibitor, bemcentinib, inhibits SARS-CoV-2 infection and represents a potential therapy for COVID-19.

**Methods:** Viral infection and host transcriptional responses to infection with SARS-CoV-2 or a VSV pseudovirus bearing SARS-CoV-2 spike were measured in human airway epithelial cell lines, engineered hACE2-expressing A549 lung cancer cells, and Vero E6 cells treated with bemcentinib or protease inhibitors. Studies also measured the effect of bemcentinib on SARS-CoV-2 binding and internalization into cells. The in vivo effect of bemcentinib (50mg/kg, orally, twice daily) was assessed in C57BL/6J mice infected with the murine coronavirus, mouse hepatitis virus (MHV, 500 or 5x10<sup>4</sup> infectious units intraperitoneally). Viral titers and loads in liver were evaluated at day 5 post-

infection. Spleen and liver were harvested to evaluate type 1 IFN-related gene expression changes.

**Results:** Bemcentinib prevented infection by SARS-CoV-2 as assessed by viral transcripts in RNAseq studies as well as viral load in qRT-PCR analysis of human lung epithelial, A549-hACE2 and Vero E6 cells. Bemcentinib reduced virus internalization without affecting virus binding. Further, bemcentinib inhibition correlated well with inhibitors that block endosomal acidification and cathepsin activity, consistent with AXL-mediated SARS-CoV-2 uptake into endosomes. In vivo, bemcentinib significantly inhibited murine MHV liver titers and virus load and significantly enhanced signatures of type I IFN response.

**Conclusion:** The orally bioavailable AXL inhibitor bemcentinib demonstrated potent antiviral effects in pre-clinical SARS-CoV-2 and other coronavirus models. These data support two ongoing phase 2 studies (EudraCT 2020-001736-95 [UK] & CTRI/2020/10/028602 [India] and DOH-27-092020-6170 [South Africa]) of bemcentinib for the treatment of COVID-19 in hospitalized patients, including those requiring supplemental oxygen and/or non-invasive ventilation, but not intubation.

### 390 MULTICENTER, OPEN-LABELED EFFICACY STUDY OF AVIFAVIR IN PATIENTS WITH COVID-19

**Suzana Corritori**<sup>1</sup>, Elena Yakubova<sup>1</sup>, Andrey Ivashchenko<sup>2</sup>, Tagir Sitdekov<sup>3</sup>, Alina Egorova<sup>4</sup>, Elena Merkulova<sup>4</sup>, Andrew Blinow<sup>5</sup>, Nikita Lomakin<sup>6</sup>, Elena Smolyarchuk<sup>7</sup>, Natalia Papazova<sup>8</sup>, Dmitry Kravchenko<sup>8</sup>, Sergey Baranovsky<sup>9</sup>, Jenny Remeeva<sup>9</sup>, Nikolay Savchuk<sup>9</sup>, Alexandr Ivachtchenko<sup>8</sup>

<sup>1</sup>Viriom, Inc, San Diego, CA, USA, <sup>2</sup>ChemRar High-Tech Center, Khimki, Russian Federation, <sup>3</sup>Russian Direct Investment Fund, Moscow, Russian Federation, <sup>4</sup>IPHARMA, Moscow, Russian Federation, <sup>5</sup>Chromis, LLC, Moscow, Russian Federation, <sup>6</sup>Central Clinical Hospital with Polyclinic, Moscow, Russian Federation, <sup>7</sup>I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation, <sup>8</sup>Chemical Diversity Research Institute, Khimki, Russian Federation, <sup>9</sup>Viriom, Inc, San Diego, CA

**Background:** Avifavir® (favipiravir 200mg tablet formulation) is the first effective direct antiviral drug approved for treatment of mild to severe COVID-19 patients. It is registered in Russia and conditionally approved in several Latin American and Asian countries. This study is a multicenter, open-labeled, comparative clinical study to assess efficacy of Avifavir in patients with COVID-19. The data represent results of post-registration real life practice of AVIFAVIR compared with the Standard-of-Supportive-Care. The analysis included data on 940 patients, of which 470 patients were included in each of the treatment groups.

**Methods:** The average age of patients was 54.9±17.5 and 55.5±19.3 years in AVIFAVIR and SOC groups respectively. 246 (52.3%) patients in AVIFAVIR group and 265 (56.4%) patients in SOC group were female. The average duration of the disease from the onset of the first symptoms to the start of therapy was 4.9±2.5 days in the AVIFAVIR group and 4.7±2.8 days in the SOC group. The average value of saturation index (SpO<sub>2</sub>, %) in AVIFAVIR group was 94.5±4.8 and in SOC group 94.3±6.6.

**Results:** Evaluation of the efficacy of AVIFAVIR was carried out in comparison with SOC for the following indicators in patients hospitalized with COVID-19: time to virus elimination; time of the improvement of clinical condition to satisfactory, time to normalization of clinical signs (SpO<sub>2</sub>) and the assessment of the number of responses to therapy. AVIFAVIR showed statistically significant results compared to SOC in terms of faster virological response; more rapid improvement of the clinical condition and higher response rates to therapy. The median time to virus elimination in the AVIFAVIR group was 6 days, while 12 days in the SOC group (which is a statistically significant difference, p<0.001). The median time to normalization of saturation (≥95%) in the AVIFAVIR group was 2 days, vs 4 days in the SOC group (p=0.001). The median time to clinical improvement was 8 days in the AVIFAVIR group and 15 days in the SOC group (p<0.001). The number of responses to therapy in the AVIFAVIR group was statistically significantly higher than in the SOC group after 5 days (p=0.0248) and after 14 days (p<0.001).

**Conclusion:** The study demonstrated the high clinical efficacy and tolerability of an early antiviral therapy with Avifavir. The results show with statistical significance that an early initiation of antiviral therapy with Avifavir is one of major factors in successful treatment and cure of COVID-19 patients.

### 391 CASE SERIES: TREATMENT OF COVID-19 WITH CONVALESCENT PLASMA IN B-CELL DEPLETION

**Arvind Gharbharan**<sup>1</sup>, Carlijn Jordans<sup>1</sup>, Susanne Bogers<sup>1</sup>, Corine H. Geurts van Kessel<sup>1</sup>, Casper Rokx<sup>1</sup>, Bart J. Rijnders<sup>1</sup>

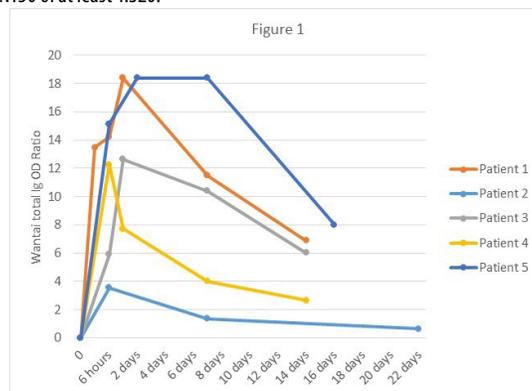
<sup>1</sup>Erasmus University Medical Center, Rotterdam, Netherlands

**Background:** Anti-CD 20 therapy is widely used in the treatment of autoimmune and hematological diseases. An absent antibody response to COVID-19 puts patients at high risk for a poor outcome or a protracted disease course. These patients may benefit from antibody-based therapy. We describe our experience with convalescent plasma (ConvP) as a source of antibody-based therapy in 5 consecutive B-cell depleted patients admitted with COVID-19.

**Methods:** B-cell depleted patients with PCR confirmed COVID-19, symptomatic for at least 12 days were informed about the possibility of ConvP therapy. ConvP was selected based on virus neutralizing antibody titers (PRNT50 using a whole SARS-CoV-2 neutralization assay) of 1:160 or higher. 300 or 600mL was transfused and in non-responders 600mL ConvP was repeated when no clinical response was observed. SARS-CoV-2 antibodies (Wantai ELISA detecting SARS-CoV-2 RBD antibodies and PRNT50) were measured preceding and after transfusion.

**Results:** 5 B-cell depleted patients were admitted to a general COVID-19 ward. B-cell depletion was the result of rituximab (n=4) and blinatumomab (n=1) for lymphoma, auto-immune disease or Acute Lymphoblastic Leukemia. They had been sick with COVID-19 for a median of 33 days (Range 13 – 84 days). All had a serum PRNT50 titer <1:20 and were without detectable antibodies against RBD by a Wantai ELISA on the day of transfusion. 1 patient received 300mL and 4 patients received 600mL of ConvP on day 1 with a median PRNT50 titer in donor plasma of 1:640 (Range 1:160 – 1:1280). All patients showed obvious clinical improvement after the first transfusion. All patients also showed pulmonary improved on a chest CT-scan. All patients seroconverted with a median PRNT50 24 hours after transfusion of 1:40 (Range 1:20 – 1:80) and a median positive Wantai total Ig OD ratio of 12.63 (range 3.55 – 18.39) (Figure 1). PCR became negative in all patients within 16 days after transfusion and isolation could be lifted at that time.

**Conclusion:** We observed prompt clinical and virological recovery after therapy with ConvP of B-cell depleted patients with a very protracted COVID-19 disease course. Our observation provide a proof of concept that in carefully selected patients, antibody-based therapy can be very effective. 24 hours after the transfusion of 600mL of ConvP, all patients had seroconverted to a PRNT50 titer of 1:20 to 1:80. We therefore suggest an initial dose of 600mL of ConvP with a PRNT50 of at least 1:320.



### 392 TREATMENT OF COVID-19 IN 22 B-CELL-DEPLETED PATIENTS

**Arvind Gharbharan**<sup>1</sup>, Carlijn Jordans<sup>1</sup>, Adam A. Anas<sup>1</sup>, Susanne Bogers<sup>1</sup>, Corine H. Geurts van Kessel<sup>1</sup>, Casper Rokx<sup>1</sup>, Bart J. Rijnders<sup>1</sup>

<sup>1</sup>Erasmus University Medical Center, Rotterdam, Netherlands

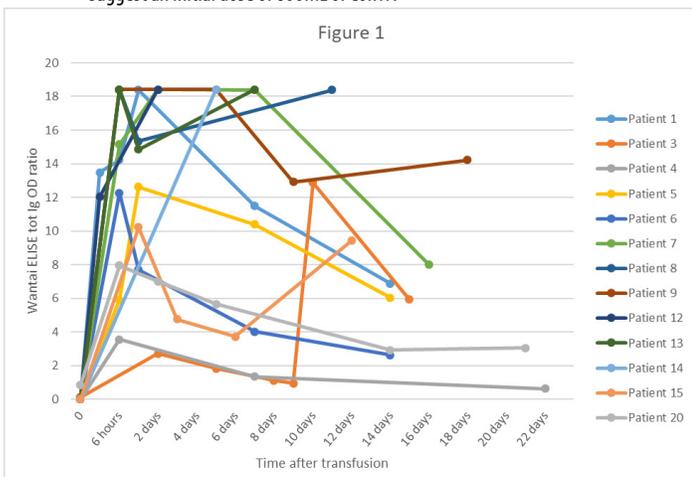
**Background:** Anti-CD20 therapy is used to treat autoimmune and hematological diseases. An absent or delayed antibody response against SARS-CoV-2 puts patients at risk for a protracted and severe disease course. These patients may benefit from antibody-based therapy of which convalescent plasma (ConvP) is the most broadly available source.

**Methods:** ConvP from donors with SARS-CoV-2 antibody titers was used when their plaque reduction neutralization test (PRNT50) showed a PRNT50 titer of at least 1:160. When PRNT50 results were not yet available, an in-house RBD ELISA was used to select the donors with the 10% highest titers. Preceding and

following transfusion, SARS-CoV-2 antibodies were measured (Wantai Ig SARS-CoV-2 RBD antibodies and PRNT50). All but 6 patients received 2 units of 300mL of ConvP. Two non-responders received a second 2x300ml transfusion while 5 patients were successfully treated with only 300ml ConvP.

**Results:** 22 B-cell depleted patients admitted with COVID-19 were treated with ConvP. B-cell depletion was the result of Rituximab (n=19), Obinutuzumab (n=1), XLA (n=1) or Blinatumomab (n=1) for lymphoma, auto-immune disease or ALL. Patients had been sick for a median of 26 days (IQR 18 – 34.5 days) and all were SARS-CoV-2 RBD antibody negative on the day of transfusion. The plasma units had a median PRNT50 titer of 1:640 (IQR 1:160 – 1:1280). 19 of 22 patients showed clear clinical improvement after transfusion and could be discharged from the hospital. 3 patients died of which 1 had treatment refractory extensive idiopathic pulmonary fibrosis preceding COVID-19. All patients seroconverted to a median total Wantai Ig OD ratio of 18.39 (IQR 11.245 – 18.41), Figure 1. PRNT50 titers increased from <1:20 preceding transfusion to 1:40 (IQR 1:20 – 1:80) after transfusion. One patient quickly recovered clinically after transfusion but it took 10 weeks to become PCR negative.

**Conclusion:** Prompt clinical and virological recovery after ConvP transfusion was observed in the large majority of B-cell depleted antibody negative patients admitted with COVID-19. Our observation shows that for carefully selected patients, antibody-based therapy can be effective. After transfusion of 600mL of ConvP, all patients had seroconverted to high anti-RBD antibody titers and detectable PRNT50 titers of 1:20 or higher. Based on these observations, we suggest an initial dose of 600mL of ConvP.



### 393 REMDESIVIR VERSUS STANDARD OF CARE FOR SEVERE COVID-19

**Susan Olender**<sup>1</sup>, Theresa L. Walunas<sup>2</sup>, Esteban Martinez<sup>3</sup>, Marta Boffito<sup>4</sup>, Katherine K. Perez<sup>5</sup>, Antonella Castagna<sup>6</sup>, Su Wang<sup>7</sup>, Parag Goyal<sup>8</sup>, Diego Ripamonti<sup>9</sup>, Jose I. Bernardino<sup>10</sup>, Richard H. Haubrich<sup>11</sup>, Anand P. Chokkalingam<sup>11</sup>, George Wu<sup>11</sup>, Helena Diaz-Cuervo<sup>12</sup>, Diana Brainard<sup>11</sup>

<sup>1</sup>Columbia University, New York, NY, USA, <sup>2</sup>Northwestern University, Chicago, IL, USA, <sup>3</sup>Hospital Clinic of Barcelona, Barcelona, Spain, <sup>4</sup>Chelsea and Westminster Hospital, London, UK, <sup>5</sup>Houston Methodist Research Institute, Houston, TX, USA, <sup>6</sup>Vita-Salute San Raffaele University, Milan, Italy, <sup>7</sup>Saint Barnabas Medical Center, Livingston, USA, <sup>8</sup>Weill Cornell Medicine, New York, NY, USA, <sup>9</sup>ASST Papa Giovanni XXIII, Bergamo, Italy, <sup>10</sup>Hospital La Paz Institute for Health Research, Madrid, Spain, <sup>11</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>12</sup>Gilead Sciences, Madrid, Spain

**Background:** Remdesivir (RDV), a direct-acting nucleotide pro-drug inhibitor of viral RNA-dependent RNA polymerases, was approved by the FDA for the treatment of hospitalized patients (pts) with COVID-19 infection and has been shown to shorten time to recovery and improve clinical outcomes in randomized clinical trials. We present the final Day 28 (D28) analysis of RDV vs standard of care (SOC) (interim Day 14 [D14] analysis published [Olender et al. Clin Infect Dis 2020]).

**Methods:** Final comparative analysis from two studies: a prospective phase 3, randomized study of RDV (RDV cohort) and a real-world retrospective cohort study of SOC (non-RDV cohort). Both studies enrolled pts with SARS-CoV-2 infection confirmed by polymerase chain reaction, who had oxygen saturation ≤94% on room air or required supplemental oxygen and had pulmonary infiltrates. Pts in the RDV cohort were randomized 1:1 to receive IV RDV for 5 or 10 days (200 mg on Day 1 followed by 100 mg/day on Days 2–5 or 2–10),

plus SOC; the two randomized dose-groups were combined for analysis. Pts in the non-RDV cohort received SOC as determined by local treatment practices (excluding RDV). Analysis populations were balanced using propensity score (PS) matching. The coprimary endpoints were D14 clinical recovery (determined using a 7-point ordinal scale) and D28 all-cause mortality. Factors associated with D28 mortality were assessed using a multivariable logistic regression model.

**Results:** After PS matching, baseline characteristics were generally similar in the RDV and non-RDV cohorts; median age 61 years, 63% male, 42% obese, 12% Black, 71% no/low-flow oxygen use, 25% high-flow oxygen, 3% ventilated. Pts in the RDV cohort had significantly higher D14 clinical recovery rates (65% vs 57%) and significantly lower D28 mortality rates (12% vs 16%) compared with the non-RDV cohort (Table). In the multivariable analysis, in addition to RDV use, a lower risk of death at D28 was associated with: younger age; being female; being White (versus being Black/African American); receiving an HIV protease inhibitor prior to baseline; not having cardiovascular disease or COPD; more days of symptoms prior to baseline; and being on room air or low-flow oxygen at baseline (versus being on invasive mechanical ventilation).

**Conclusion:** RDV was associated with significantly higher rates of clinical recovery at Day 14 and lower Day 28 mortality compared with SOC in hospitalized pts with severe SARS-CoV-2 infection.

Table: Clinical recovery and mortality rates in hospitalized patients with severe SARS-CoV-2 infection (based on PS matching)

|                                   | RDV cohort<br>N = 368 | Non-RDV cohort<br>N = 1399 | Odds ratio<br>[95% confidence interval],<br>P value* |
|-----------------------------------|-----------------------|----------------------------|--|
| Day 14 clinical recovery, n/N (%) | 240/368 (65.2)        | 798/1398 (57.1)            | 1.49<br>[1.16–1.90],<br>0.0017                       |
| Day 28 mortality, n/N (%)         | 44/368 (12.0)         | 226/1399 (16.2)            | 0.67<br>[0.47–0.95],<br>0.026                        |

\*P value, odds ratio and 95% confidence interval were based on the generalized estimating equation with matched sets considered as clusters. PS used 1:10 greedy matching with a caliper distance of 0.25; matching based on duration of symptoms prior to baseline, age (<40 years, 40–64 years, and ≥65 years), sex, race (Asian, Black, Other, and White), country of enrolment (Italy, Spain, USA, and Other), obesity, clinical status ordinal scale score, comorbidities (hypertension, cardiovascular disease, diabetes mellitus, COPD, asthma), and non-RDV potential COVID-19 medications (azithromycin, biologics, HIV protease inhibitors, hydroxychloroquine, and ribavirin) taken at/prior to baseline.

RDV cohort: NCT04292899/GS-US-540-5773; Non-RDV cohort: EUPAS34303/GS-US-540-5807

### 394 COBICISTAT SYNERGIZES WITH REMDESEVIR TO SUPPRESS SARS-CoV-2 REPLICATION IN VITRO

**Iart Luca Shytaj**<sup>1</sup>, Mahmoud M. Tolba<sup>2</sup>, Bojana Lucic<sup>1</sup>, Lara Gallucci<sup>1</sup>, Mohamed Fares<sup>3</sup>, Liv Zimmermann<sup>4</sup>, Ahmed Taha Ayoub<sup>5</sup>, Vitor Laketa<sup>4</sup>, Petr Chlanda<sup>4</sup>, Oliver T. Fackler<sup>1</sup>, Boulant Steeve<sup>6</sup>, Ralf Bartenschlager<sup>6</sup>, Megan Stanifer<sup>6</sup>, Andrea Savarino<sup>7</sup>, Marina Lusic<sup>1</sup>

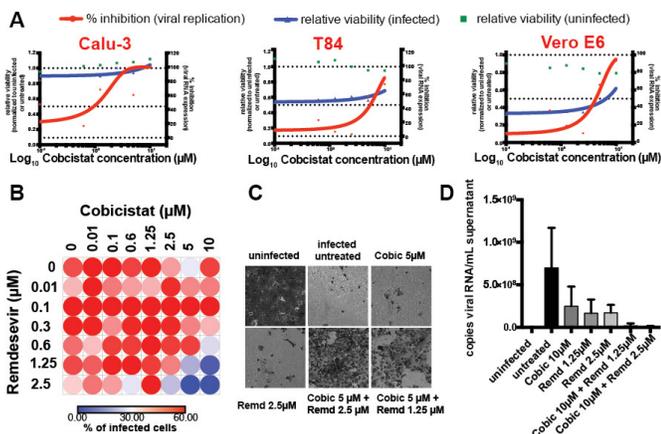
<sup>1</sup>Department of Infectious Diseases, Integrative Virology, CIID, Heidelberg University Hospital, Heidelberg, Germany, <sup>2</sup>Pharmaceutical Unit, Ministry of Health and Population, Faiyum, Egypt, <sup>3</sup>Department of Hydrobiology, Veterinary Research Division, National Research Centre, Cairo, Egypt, <sup>4</sup>Department of Infectious Diseases, Virology, CIID, Heidelberg University Hospital, Heidelberg, Germany, <sup>5</sup>Department of Pharmaceutical Chemistry, Heliopolis University, Cairo, Egypt, <sup>6</sup>Department of Infectious Diseases, Molecular Virology, CIID, Heidelberg University Hospital, Heidelberg, Germany, <sup>7</sup>Department of Infectious and Immune-Mediated Diseases, Italian Institute of Health, Rome, Italy

**Background:** The ongoing SARS-CoV-2 pandemic poses an urgent need to identify novel drug treatments that are effective, well tolerated and quickly translatable to a clinical setting.

**Methods:** In-silico binding modes were predicted by molecular docking. The Bavpat<sub>1/2</sub> SARS-CoV-2 isolate was used to infect Calu-3, T84, Vero E6 cells and a primary colon organoid at MOIs of 0.05 or 0.5. Supernatant and intracellular SARS-CoV-2 RNA was quantified by RT-qPCR or immunofluorescence (IF). The activity of the main protease of SARS-CoV-2 (3CLpro) was measured by FRET assay. Viral protein expression was assessed by western blot. Syncytia formation was determined by IF in cells expressing the spike protein. Cell viability was determined by MTT and crystal violet staining. Synergism scores were calculated using the SynergyFinder web-tool.

**Results:** In-silico docking using a library of FDA-approved drugs highlighted cobicistat as candidate inhibitor of SARS-CoV-2 3CLPro. Experiments using two different viral MOIs in three different cell lines proved that cobicistat inhibits SARS-CoV-2 replication at non-toxic, low micromolar concentrations (IC<sub>50</sub> 0.6–9 μM; CC<sub>50</sub> 39–52 μM) (Fig 1A). However, cobicistat did not inhibit 3CLpro activity in FRET assay, while western blot analysis suggested that cobicistat

impacts on spike glycoprotein levels/processing. Accordingly, cobicistat decreased syncytia formation in spike-expressing Vero E6 cells. The range of in-vitro antiviral concentrations of cobicistat was compatible with plasma levels reachable in mice and humans, but above those achieved through standard dosages used to boost HIV-1 protease inhibitors, in line with the failure of trials testing cobicistat-boosted darunavir on SARS-CoV-2 patients. As the booster activity of cobicistat is exerted through inhibition of Cytochrome P4503A (CYP3A) and P-glycoprotein P-gp (known also as multidrug resistance MDR1), we combined it with remdesivir, which is a putative CYP3A and P-gp substrate. The drug combination was able to synergistically rescue the viability of infected cells to levels comparable to uninfected controls and to almost entirely abrogate viral replication in two cell lines and a primary colon organoid (Figure 1B-D). **Conclusion:** Cobicistat and remdesivir synergistically inhibit SARS-CoV-2 replication and cytopathic effects. Cobicistat can form the backbone of combination treatments due to its dual activity as direct antiviral and pharmacoenhancer.



**Figure.** Panel A) Effect of cobicistat on the inhibition of SARS-CoV-2 replication (red), mortality of infected cells (blue), and the viability of uninfected cells (green). The Calu-3, T84 and Vero E6 cell lines were infected at 0.05 MOI and treated with cobicistat 2h post-infection. Viral RNA in supernatants and cell viability were measured 48h post-treatment. Panels B-D) Synergistic effect of the combination of cobicistat and remdesivir in inhibiting SARS-CoV-2 replication and rescuing viability of Vero E6 cells infected at 0.5 MOI. Levels of SARS-CoV-2 RNA were detected by IF (Panel B) or qPCR (panel D). Viable cells were estimated by staining with crystal violet following fixation in 4% PFA (panel C).

**395 ACUTE KIDNEY INJURY IN PATIENTS WITH MODERATE COVID-19 TREATED WITH RDV VERSUS SoC**

**Onyema Ogbuagu<sup>1</sup>,** Karen T. Tashima<sup>2</sup>, Huldrych F. Günthard<sup>3</sup>, Mark McPhail<sup>4</sup>, Arun J. Sanyal<sup>5</sup>, Emon Elboudwarej<sup>6</sup>, Yuan H. Tian<sup>6</sup>, Laura H. Telep<sup>6</sup>, Susanna K. Tan<sup>6</sup>, Anand P. Chokkalingam<sup>6</sup>, Anu O. Osinus<sup>6</sup>, Diana Brainard<sup>6</sup>, Robert L. Gottlieb<sup>7</sup>, Antonella Castagna<sup>8</sup>, Judith A. Aberg<sup>9</sup>

<sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>The Miriam Hospital, Providence, RI, USA, <sup>3</sup>University Hospital Zurich, Zurich, Switzerland, <sup>4</sup>King's College Hospital NHS Foundation Trust, London, UK, <sup>5</sup>Virginia Commonwealth University Medical Center, Richmond, VA, USA, <sup>6</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>7</sup>Baylor University Medical Center, Dallas, TX, USA, <sup>8</sup>Ospedale San Raffaele, Milano, Italy, <sup>9</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA

**Background:** Remdesivir (RDV), an RNA-dependent RNA polymerase inhibitor of SARS-CoV-2, and its intravenous formulation excipient, cyclodextrin, are renally cleared. We sought to characterize whether RDV was associated with worsening renal function in hospitalized patients with moderate COVID-19.

**Methods:** We conducted an open-label, phase 3 trial (NCT04252664) involving hospitalized patients with confirmed SARS-CoV-2 infection, evidence of pulmonary infiltrates, oxygen saturation >94% on room air and eGFR ≥50 mL/min/1.73m<sup>2</sup>. Patients were randomly assigned 1:1:1 to receive up to 5d or 10d of RDV with standard of care (SoC), or SoC alone. Also included in this analysis were patients who enrolled in an extension phase of the trial, receiving 10d of RDV. RDV was dosed intravenously at 200 mg on d1 and 100 mg daily thereafter. Acute kidney injury (AKI) was defined as an increase in serum creatinine from baseline and classified as Stage 1 (increase > 0.3 and % change ≤25%, or % change >25% and ≤ 100%), Stage 2 (% change >100% and ≤200%), Stage 3 (% change >200%). For AKI development (ever/never for stage 1 or greater), age-adjusted risk ratios (RR) and 95% Wald confidence intervals (CI) were reported.

**Results:** 1005 patients (822 [83%] RDV, 183 [17%] SoC) with creatinine values collected through d14 were evaluated. Baseline patient demographics, creatinine, and eGFR were mostly similar between RDV vs SoC arms. Worsening renal function was observed less frequently in patients receiving RDV vs SoC (7% vs 10%, p=0.03, Table). After adjustment for age, there was no significant association of RDV with risk of AKI relative to SoC (RR=0.66; 95% CI 0.40, 1.09). Most AKI events were observed in patients with baseline eGFR >90 mL/min, with few events occurring in patients with a baseline eGFR 50-59 mL/min. In patients who developed Stage 3 AKI, those treated with RDV (n=2, 0.2%) returned to baseline creatinine values while those on SoC (n=4, 2%) remained elevated to d14. No difference in AKI between treatment arms was observed in patients with a history of chronic kidney disease (CKD; RDV: n=6 [12%] vs SoC: n=2 [40%] p=0.14). Older age, history of CKD, and eGFR status at baseline were independently associated with worsening renal function. **Conclusion:** AKI events were observed less frequently in patients with moderately severe COVID-19 patients treated with RDV compared to SoC.

**Table.** AKI Event Counts and Adjusted Risk Ratios Overall and Stratified by Baseline eGFR Status

|  | Overall           |           | eGFR 50-59 mL/min |          | eGFR 60-89 mL/min |           | eGFR 90+ mL/min   |           |
|--|-------------------|-----------|-------------------|----------|-------------------|-----------|-------------------|-----------|
|  | SoC n=183         | RDV n=822 | SoC n=17          | RDV n=71 | SoC n=48          | RDV n=211 | SoC n=118         | RDV n=540 |
| <b>No AKI, n (%)</b>                   | 164 (90)          | 765 (93)  | 16 (94)           | 69 (97)  | 44 (92)           | 194 (92)  | 104 (88)          | 502 (93)  |
| <b>AKI, n (%)</b>                      | 19 (10)           | 57 (7)    | 1 (6)             | 2 (3)    | 4 (8)             | 17 (8)    | 14 (12)           | 38 (7)    |
| Stage 1                                | 15 (8)            | 52 (6)    | 0                 | 2 (3)    | 3 (6)             | 14 (7)    | 12 (10)           | 36 (7)    |
| Stage 2                                | 0                 | 3 (0.4)   | 0                 | 0        | 0                 | 1 (0.5)   | 0                 | 2 (0.4)   |
| Stage 3                                | 4 (2)             | 2 (0.2)   | 1 (6)             | 0        | 1 (2)             | 2 (1)     | 2 (2)             | 0         |
| Fisher's exact p-value (AKI vs no AKI) | 0.03              |           | 0.22              |          | 0.71              |           | 0.03              |           |
| Age adjusted RR (AKI vs no AKI)        | 0.66 (0.40, 1.09) |           | NC                |          | 0.96 (0.34, 2.73) |           | 0.58 (0.32, 1.04) |           |

NC= not calculated, due to low numbers of events

**396 SYMPTOM OUTCOME MEASURES FOR OUTPATIENT COVID-19 PHASE 3 TREATMENT TRIALS**

**Kara W. Chew<sup>1</sup>,** Carlee B. Moser<sup>2</sup>, Eric S. Daar<sup>1</sup>, David A. Wohl<sup>3</sup>, Eunice Yeh<sup>2</sup>, Justin Ritz<sup>2</sup>, Arzhang Cyrus Javan<sup>4</sup>, Joseph J. Eron<sup>3</sup>, Judith S. Currier<sup>1</sup>, Davey M. Smith<sup>5</sup>, Michael Hughes<sup>5</sup>, for the ACTIV-2/A5401 Study Team

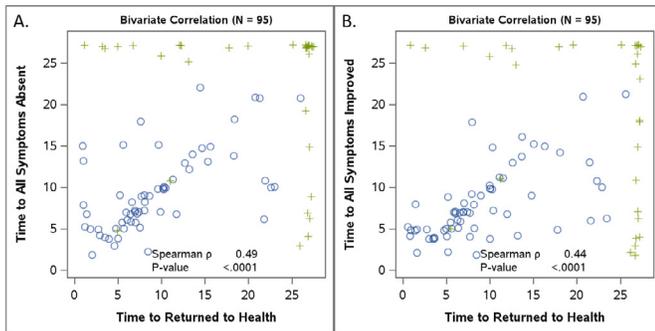
<sup>1</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>4</sup>National Institutes of Health, Rockville, MD, USA, <sup>5</sup>University of California San Diego, La Jolla, CA, USA

**Background:** Due to the substantial morbidity but low rates of hospitalization and death among outpatients with COVID-19, symptom outcome measures should be considered for primary efficacy assessment in phase 3 treatment trials. We analyzed potential measures utilizing the ACTIV-2 participant diary. **Methods:** Data from the first 95 participants in ACTIV-2 were included. All had symptomatic SARS-CoV-2 infection and received blinded bamlanivimab 7000 mg/placebo. The symptom diary was completed by participants prior to treatment (Day 0) and then daily for 28 days. It included 13 targeted symptoms scored as absent, mild, moderate, or severe, and a question about whether they had returned to pre-COVID-19 health. Without unblinding, 3 candidate symptom outcome measures were assessed: A) time to confirmed (2 consecutive days) absence of all targeted symptoms, B) time to all targeted symptoms confirmed to be mild or absent, and C) time to confirmed improvement in all targeted symptoms. Median time to outcome was estimated by Kaplan-Meier methods.

**Results:** Of the 95 participants, 53% were female, 82% white, and 33% Latinx. Median age was 44 years; 46% were age ≥55 years and/or had protocol-defined comorbidities. Median time from COVID-19 symptom onset to randomization was 6 days. Prevalence of each targeted symptom on Day 0 ranged from 6% vomiting to 87% fatigue. Candidate outcome B was met in median 2 days due to 29% of participants having only mild symptoms at Day 0. For candidate outcomes A and C, median time was 11 and 8 days, with 26% and 16%, respectively, not meeting the outcome by 28 days. These candidate outcomes (A and C) were associated with a participant's confirmed assessment of return to pre-COVID-19 health (Figure). For all measures, increasing the consecutive days required for confirmation from 2 to 3 or 4 had a modest impact on median time to the outcome being met, consistent with few participants experiencing relapsing symptoms.

**Conclusion:** Outcomes based on symptom resolution (A) or improvement (C) are promising for evaluating COVID-19 treatment response, with good internal validity with self-assessment of return to pre-COVID-19 health. A valid symptom outcome measure may be preferred over hospitalization/death as a primary outcome for outpatient COVID-19 treatment trials as most participants achieve the outcome, increasing power to compare treatments, especially among participants who are at low risk for hospitalization/death.

**Figure.** Spearman correlations between candidate outcome measure A (time (days) to all targeted symptoms absent for 2 consecutive days) and time to return to pre-COVID-19 health (A) and between candidate outcome measure C (time (days) to all targeted symptoms improved for 2 consecutive days) and time to return to pre-COVID-19 health (B). Blue circles = participants with observed times for both outcomes; green plus signs = participants with censored times for one or both outcomes.



### 397 TREATMENT AND OUTCOMES OF COVID-19 IN THE US: ARE THEY DIFFERENT ACCORDING TO RACE?



Essy Mozaffari<sup>1</sup>, Aastha Chandak<sup>2</sup>, Shuting Liang<sup>1</sup>, Julie Gayle<sup>3</sup>, Mark Thrun<sup>1</sup>, Paul Hodgkins<sup>1</sup>, Richard H. Haubrich<sup>1</sup>

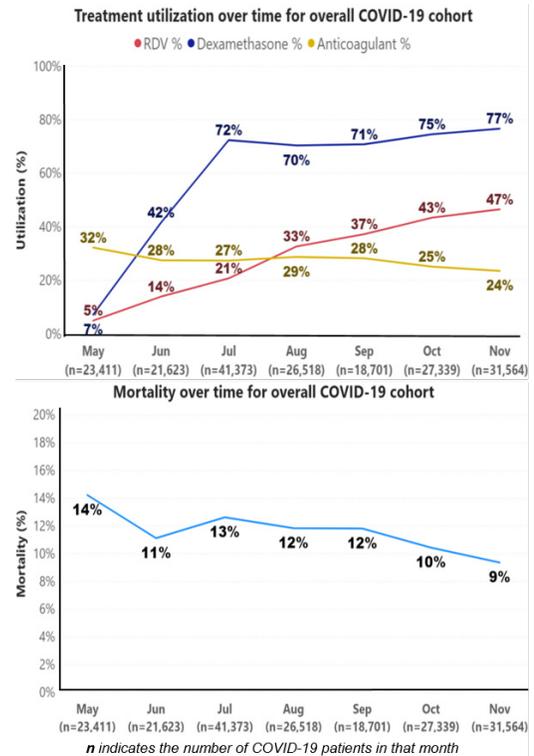
<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>2</sup>Certara, New York, NY, USA, <sup>3</sup>Premier, Inc., Charlotte, NC, USA

**Background:** Clinical practice patterns for hospitalized COVID-19 patients have rapidly evolved, including specific treatment utilization. In turn, outcomes including time to improvement and mortality have also changed, but some reports have shown disproportionate mortality in Blacks. Data on the use of COVID-19 treatments over time and temporal association with hospital mortality and length of stay (LOS), along with assessments by race, are lacking.

**Methods:** This was a retrospective cohort study of adult patients with a discharge diagnosis of COVID-19 (ICD-10-CM: U07.1) admitted between May-Nov 2020 using the chargemaster inpatient data from the Premier Healthcare Database. Demographic characteristics of the cohort were summarized. Utilization of remdesivir (RDV), dexamethasone, anticoagulants, tocilizumab, sarilumab and baricitinib were examined. Median hospital and intensive care unit (ICU) LOS were assessed over time. In-hospital mortality was identified through discharge status. Unadjusted mortality rates over time are reported.

**Results:** Between May-Nov 2020, 190,529 patients were hospitalized for COVID-19 in 823 US hospitals. Patients had a mean age of 64 years, 64% were White, 19% Black, 53% male and 65% had Medicare/ Medicaid as primary payor. Black patients were younger than White (mean 60 vs. 66 years). Significant comorbidities (>20%) were similar between overall cohort and Black patients and included chronic pulmonary disease, hypertension and obesity. From May to Nov, overall RDV utilization increased from 5% to 47%, dexamethasone utilization increased from 7% to 77% and anticoagulant treatment utilization decreased from 32% to 24% (Figure). Few patients received tocilizumab (5%), sarilumab (0.02%) and baricitinib (0.003%). Among Black patients, RDV use increased from 5% to 39% and dexamethasone use increased from 6% to 74%. The median LOS of the overall cohort and Black cohort decreased from 6 days in May to 5 days in Nov, and overall ICU LOS for patients decreased from 5 to 4 days during this time; 5 to 3 in Black patients. Overall in-hospital mortality rate decreased by 35%, and by 38% in Black patients.

**Conclusion:** In US hospitalized patients, use of both dexamethasone and RDV has increased approximately 10-fold from May to Nov. Over this same time, a 35% reduction in mortality, a 17% reduction in LOS and 20% reduction in ICU stay were observed. Besides age, no notable differences were apparent by race. Understanding the drivers of improvement in outcomes requires further analyses.



### 398 TENOFOVIR DIPHOSPHATE IN DRIED BLOOD SPOTS PREDICTS FUTURE VIREMIA IN SOUTH AFRICA

Reuben N. Robbins<sup>1</sup>, Lauren Jennings<sup>2</sup>, Nadia Nguyen<sup>3</sup>, Christopher Ferraris<sup>1</sup>, Cheng-Shiun Leu<sup>4</sup>, Curtis Dolezal<sup>1</sup>, Marvin Hsiao<sup>5</sup>, Ofole Mgbako<sup>4</sup>, John Joska<sup>6</sup>, Jose R. Castillo-Mancilla<sup>7</sup>, Landon Myer<sup>6</sup>, Peter Anderson<sup>7</sup>, Catherine Orrell<sup>2</sup>, Robert Remien<sup>1</sup>

<sup>1</sup>New York State Psychiatric Institute, New York, NY, USA, <sup>2</sup>Desmond Tutu HIV Foundation, Cape Town, South Africa, <sup>3</sup>Columbia University, New York, NY, USA, <sup>4</sup>Columbia University Medical Center, New York, NY, USA, <sup>5</sup>National Health Laboratory Service, Cape Town, South Africa, <sup>6</sup>University of Cape Town, Cape Town, South Africa, <sup>7</sup>University of Colorado, Aurora, CO, USA

**Background:** Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is a powerful biomarker of cumulative ART adherence. While some data demonstrate the value of this measure to predict future viremia, no data in African persons living with HIV (PLWH) are available. We examined the ability of TFV-DP in DBS to predict future viral breakthrough in South African PLWH.

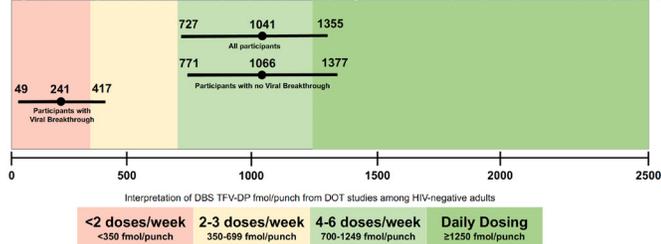
**Methods:** We enrolled 250 PLWH ( $\geq 18$  years of age) from 4 primary health clinics in Cape Town receiving tenofovir disoproxil fumarate (TDF)-based regimens (for 4 to 24 months) who had an undetectable (<50 copies/mL) HIV viral load (VL). Paired HIV VL and DBS for TFV-DP were collected monthly for 12 months. Viral breakthrough was defined as the first HIV VL >400 copies/mL. Receiver operating characteristics (ROC) analysis identified the TFV-DP threshold that best predicted viral breakthrough at the next monthly visit and generalized estimating equations to estimate the odds ratio and 95% confidence intervals (95% CI) for this association.

**Results:** Participants provided 2,944 paired DBS and HIV VL samples. Mean (SD) age was 35.52 (10.42) years; mean duration on ART at study entry was 10 (5) months; 78% were women. Median (IQR) study visits completed was 13 [12,13]. Median overall TFV-DP concentration was 1,041 (727, 1355) fmol/punch. Twenty-one participants developed viral breakthrough, with a median VL of 9,505 (1,430, 45,481) copies/mL, and TFV-DP concentrations of 241 (49, 417) fmol/punch at the first breakthrough (Figure). A threshold TFV-DP concentration in DBS of 400 fmol/punch maximized sensitivity and specificity to detect future viral breakthrough. Participants with TFV-DP  $\leq 400$  fmol/punch had 32 times the odds (95% CI: 18, 57;  $p < 0.001$ ) of developing future viral breakthrough one month later compared to participants with TFV-DP >400 fmol/punch.

**Conclusion:** TFV-DP in DBS strongly predicted future viral breakthrough the following month in South African PLWH. These results are consistent with data established in US PLWH, although TFV-DP threshold concentrations were lower in this population, possibly due to biologic differences in study populations, use

of generic TDF, or how viral breakthrough was defined (>400 copies/mL). Future studies exploring the use of this adherence biomarker to clinically manage and provide timely feedback to PLWH are warranted.

Figure. Median (25%, 75%) tenofovir-diphosphate (TFV-DP) drug concentrations (fmol/punch) in dried blood spots (DBS)



### 399 EFFECTIVENESS OF THE DOLUTEGRAVIR TRANSITION IN UGANDA: DISCO COHORT WEEK-24 RESULTS

**Suzanne McCluskey**<sup>1</sup>, Winnie Muyindike<sup>2</sup>, Daniel Omoding<sup>2</sup>, Godfrey Masette<sup>2</sup>, Ashley Stuckwisch<sup>1</sup>, Bethany Hedt-Gauthier<sup>3</sup>, Vincent Marconi<sup>4</sup>, Mahomed-Yunus Moosa<sup>5</sup>, Deenan Pillay<sup>6</sup>, Ravindra Gupta<sup>7</sup>, Mark Siedner<sup>1</sup>, for the Mwebesa Bwana Research Group

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>Mbarara University of Science and Technology, Mbarara, Uganda, <sup>3</sup>Harvard Medical School, Boston, MA, USA, <sup>4</sup>Emory University, Atlanta, GA, USA, <sup>5</sup>University of KwaZulu-Natal, Durban, South Africa, <sup>6</sup>University College London, London, UK, <sup>7</sup>Cambridge University, Cambridge, UK

**Background:** The fixed-dose combination of tenofovir (TDF), lamivudine (3TC), and dolutegravir (TLD) is now preferred first-line antiretroviral therapy (ART) for most adults with HIV in Sub-Saharan Africa. Yet, concerns remain about durability of TLD with high circulating resistance to 3TC and TDF and metabolic abnormalities observed in clinical trials. Limited programmatic data are available to describe the success of the TLD transition in the region.

**Methods:** We established the DISCO cohort to quantify viral suppression and regimen tolerability during the TLD transition. We prospectively enrolled adults from public clinics in Uganda and South Africa who had been on non-nucleoside reverse transcriptase inhibitor-based ART for ≥6 months and were programmatically switched to TLD. We obtained demographics, medical history data, and plasma specimens at enrollment and week 24. We conducted retrospective HIV-1 RNA viral load (VL) testing using the Cepheid GeneXpert platform. Though both sites were interrupted by COVID-19, here we report complete week 24 results for the Uganda cohort.

**Results:** We enrolled 500 participants (41% female) in Uganda. Median age was 47 years (IQR 40 – 53). Median ART duration was 8.8 years (IQR 5.7 – 12.2). The most common regimens prior to TLD switch were 3TC/TDF/efavirenz (44%) and 3TC/zidovudine/nevirapine (39%). Retrospective VL testing demonstrated that 95% (475/499) had VL <50 copies/mL, 4% (19/499) had VL 50-1,000 copies/mL, and 1% (5/499) had VL >1,000 copies/mL at enrollment. 90% (448/500) completed week 24 visits, with 50 additional visits delayed during COVID-19, 1 disenrollment, and 1 death. By week 24, 1% (6/448) discontinued TLD due to side effects or clinician discretion. At week 24, 96% (432/448) had VL <50 copies/mL, 3% (12/448) had VL 50–1,000 copies/mL, and 1% (4/448) had VL >1,000 copies/mL. Of those with week 24 VL >50 copies/mL, 31% (5/16) had detectable VL >50 copies/mL at enrollment, versus 3% (15/431) in those with suppressed VL at week 24 ( $\chi^2$  p-value<0.001).

**Conclusion:** The great majority of participants transitioned to TLD with an undetectable VL. Overall, we documented 86% suppression at week 24 after TLD switch in the midst of the COVID-19 pandemic and 96% suppression in those completing a week 24 visit. These data support early tolerability and efficacy of TLD transition in the public sector. However, detectable VL at switch predicted detectable VL at 24 weeks. Vigilance and programmatic monitoring are needed to ensure long-term durability of TLD.

### 400 DOLUTEGRAVIR IN REAL LIFE: QUALITY-OF-LIFE OUTCOMES IN A COHORT STUDY IN LESOTHO

**Jennifer A. Brown**<sup>1</sup>, Bienvenu L. Nsakala<sup>2</sup>, Kuen Mokhele<sup>2</sup>, Itumeleng Rakuoane<sup>2</sup>, Reitumetse Peea<sup>3</sup>, Tapiwa Tarumbiswa<sup>4</sup>, Josephine Muhairwe<sup>2</sup>, Tracy R. Glass<sup>1</sup>, Alain Amstutz<sup>1</sup>, Nadine Bachmann<sup>1</sup>, Jennifer M. Belus<sup>5</sup>, Thomas Klimkait<sup>6</sup>, Niklaus D. Labhardt<sup>1</sup>

<sup>1</sup>Swiss Tropical and Public Health Institute, Basel, Switzerland, <sup>2</sup>SolidarMed, Maseru, Lesotho, <sup>3</sup>Butha-Buthe Government Hospital, Maseru, Lesotho, <sup>4</sup>Ministry of Health, Maseru, Lesotho, <sup>5</sup>University of Maryland, College Park, College Park, MD, USA, <sup>6</sup>University of Basel, Basel, Switzerland

**Background:** Following the World Health Organization 2018 interim guidance, HIV programs in low-resource settings routinely transition individuals taking efavirenz (EFV) based first-line antiretroviral therapy (ART) to dolutegravir (DTG) containing ART. As both drugs are associated with neuropsychological side-effects, this prospective cohort study assesses mental health as well as common HIV/ART-related symptoms before and after transition from EFV to DTG in Lesotho.

**Methods:** The Dolutegravir in Real Life in Lesotho cohort enrolls people living with HIV transitioning to or initiating DTG-based therapy (NCT04238767).

Here, we report results of adult participants undergoing a programmatic transition from EFV to DTG at Buthe-Buthe Government Hospital, Lesotho. At baseline (day of transition from EFV to DTG) and follow-up (16 weeks [10-24 weeks] after transition), participants were interviewed using the Patient Health Questionnaire-9 (PHQ-9) to screen for depression, and a modified HIV symptom index (mHSI) questionnaire containing 21 pre-specified symptoms. Enrolment began on Feb 10, 2020 and data was closed for this analysis on Nov 16, 2020. Differences in PHQ-9 outcomes and mHSI symptoms before and after the transition were assessed using the marginal homogeneity test and the McNemar test, respectively. In addition, we report results stratified by gender.

**Results:** At data closure, 664 participants had completed follow-up, 339/664 (60.1%) were female, median age was 47 years (IQR 38-56), and median time on ART was 5.5 years (IQR 3.3-8.8). Baseline and follow-up PHQ-9 data were available for 662/664 participants. In both genders, the proportion reporting at least mild depression symptoms (score ≥5) nearly halved after transition to DTG (59/661 [8.9%] vs 32/661 [4.8%]; table). mHSI data were available for 649/664 participants. The sum of reported symptoms across all individuals decreased from 821 at baseline to 597 at follow-up. The frequency of reporting changed significantly in five mHSI symptoms, all of which decreased after transition to DTG. The greatest change was observed for feeling nervous/anxious (table).

**Conclusion:** In this ART-experienced adult population in Lesotho, the prevalence of reported depressive as well as psychosomatic symptoms decreased after routine transition from EFV to DTG-containing ART. The WHO recommendation to shift from EFV to DTG as first-line ART in low-resource settings may thus not only improve viral suppression but also quality of life among persons living with HIV.

|   | Total, baseline | Total, follow-up | Total, difference / unadjusted p-value | Female, baseline | Female, follow-up | Male, baseline  | Male, follow-up |
|---|-----------------|------------------|--|------------------|-------------------|-----------------|-----------------|
| <b>PHQ-9 depression score</b>                                       |                 |                  | 0.0036                                 |                  |                   |                 |                 |
| None/minimal (score 0-4)  | 605/662 (91.1%) | 630/661 (95.2%)  | 4.1%                                   | 362/398 (91.0%)  | 378/398 (95.0%)   | 241/264 (91.3%) | 252/264 (95.5%) |
| Mild (score 5-9)  | 49/662 (7.4%)   | 27/661 (4.1%)    | -3.3%                                  | 31/398 (7.8%)    | 15/398 (3.8%)     | 18/264 (6.8%)   | 12/264 (4.5%)   |
| Moderate to severe (score 10-27)                                    | 10/662 (1.5%)   | 5/661 (0.8%)     | -0.8%                                  | 5/398 (1.3%)     | 5/398 (1.3%)      | 5/264 (1.9%)    | 0               |
| <b>mHSI: proportion impacted by the symptom at least "a little"</b> |                 |                  |  |                  |                   |                 |                 |
| Fatigue or loss of energy   | 23/649 (3.5%)   | 13/649 (2.0%)    | -0.0022 (5.1%)                         | 20/393 (5.1%)    | 9/393 (2.3%)      | 13/256 (5.1%)   | 4/256 (1.6%)    |
| Trouble remembering   | 78/649 (12.0%)  | 49/649 (7.6%)    | -0.0035 (14.0%)                        | 55/393 (14.0%)   | 29/393 (7.4%)     | 23/256 (9.0%)   | 20/256 (7.8%)   |
| Felt sad, down or depressed   | 54/648 (8.3%)   | 23/648 (3.5%)    | -0.0004 (8.2%)                         | 32/392 (8.2%)    | 14/392 (3.6%)     | 22/256 (8.6%)   | 9/256 (3.5%)    |
| Felt nervous or anxious   | 68/648 (10.5%)  | 22/648 (3.4%)    | -0.0001 (10.5%)                        | 41/392 (10.5%)   | 3/392 (0.8%)      | 27/256 (10.5%)  | 8/256 (3.1%)    |
| Nightmares, strange or vivid dreams                                 | 56/649 (8.6%)   | 25/649 (3.9%)    | -0.0002 (9.2%)                         | 36/393 (9.2%)    | 18/393 (4.6%)     | 20/256 (7.8%)   | 7/256 (2.7%)    |

#### 401 WEEK 96 EFFICACY AND SAFETY OF CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M

**Hans Jaeger**<sup>1</sup>, E. Turner Overton<sup>2</sup>, Gary Richmond<sup>3</sup>, Giuliano Rizzardini<sup>4</sup>, Jaime Federico Andrade-Villanueva<sup>5</sup>, Rosie Mngqibisa<sup>6</sup>, Antonio Ocampo Hermida<sup>7</sup>, Anders Thalme<sup>8</sup>, Paul Benn<sup>9</sup>, Yuanyuan Wang<sup>10</sup>, Krischan J. Hudson<sup>11</sup>, David M. Margolis<sup>11</sup>, Christine Talarico<sup>11</sup>, Kati Vandermeulen<sup>12</sup>, William R. Spreen<sup>11</sup>  
<sup>1</sup>MVZ Karlsplatz HIV Research and Clinical Care Center, Munich, Germany, <sup>2</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>3</sup>Nova Southeastern University, Fort Lauderdale, FL, USA, <sup>4</sup>Fatebenefratelli Sacco Hospital, Milan, Italy, <sup>5</sup>Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico, <sup>6</sup>Durban International Clinical Research Site, Durban, South Africa, <sup>7</sup>Complejo Hospitalario Universitario de Vigo, Vigo, Spain, <sup>8</sup>Karolinska University Hospital, Stockholm, Sweden, <sup>9</sup>ViiV Healthcare, Brentford, UK, <sup>10</sup>GlaxoSmithKline, Collegeville, PA, USA, <sup>11</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>12</sup>Janssen, Beerse, Belgium

**Background:** The dosing frequency of cabotegravir (CAB) and rilpivirine (RPV) long-acting (LA) administered every 1 or 2 months may address challenges associated with daily oral ART, such as adherence, pill burden, and stigma. The Week (W) 48 results from ATLAS-2M (NCT03299049) demonstrated noninferiority of CAB+RPV LA administered every 8 weeks (Q8W) compared with every 4 weeks (Q4W). Here, we report the W96 results.

**Methods:** ATLAS-2M is an ongoing Phase 3b, randomized, multicenter study assessing the efficacy and safety of CAB+RPV LA Q8W vs. Q4W. Virologically suppressed individuals receiving CAB+RPV LA Q4W (ATLAS [NCT02951052] study rollover) or oral SoC were randomized 1:1 to receive CAB+RPV LA Q8W or Q4W. The primary endpoint at W48 was the proportion of participants with plasma HIV-1 RNA  $\geq 50$  c/mL (FDA Snapshot, ITT-E; 4% noninferiority margin). Endpoints assessed at W96 include proportion of participants with plasma HIV-1 RNA  $\geq 50$  c/mL and HIV-1 RNA  $< 50$  c/mL, incidence of confirmed virologic failure (CVF; two consecutive plasma HIV-1 RNA  $\geq 200$  c/mL), safety, and tolerability.

**Results:** 1045 participants received CAB+RPV LA (Q8W, n=522; Q4W, n=523). The median (range) age was 42y (19–83); 27% were female (sex at birth), and 73% were white. At W96, CAB+RPV LA Q8W confirmed noninferior efficacy to Q4W dosing, with 2.1% (n=11) and 1.1% (n=6) of participants having HIV-1 RNA  $\geq 50$  c/mL in each arm, respectively (Table 1). High levels of virologic suppression were observed across both arms, with 90–91% of participants maintaining HIV-1 RNA  $< 50$  c/mL at W96. Through W96, 9 (1.7%) and 2 (0.4%) participants in the Q8W and Q4W arms had CVF, respectively; 1 occurred between W48 and W96 (participant in Q8W arm with baseline RPV resistance-associated mutation [RAM] Y181C and no INSTI RAMs). Safety profiles were comparable between arms, with no new safety signals identified since the W48 analysis. Injection site reactions (ISRs) were the most common adverse event and led to 1 withdrawal between W48 and W96 (Q8W arm); most were mild or moderate in severity (98.6%), with a median duration of 3 days. The frequency of ISRs decreased over time (W48: Q8W, n=115/493 [23%]; Q4W, n=100/488 [20%]; W96: Q8W, n=74/473 [16%]; Q4W, n= 54/468 [12%]).

**Conclusion:** Efficacy of CAB+RPV LA Q8W continued to be noninferior to Q4W at W96, with both regimens maintaining high levels of virologic suppression. These longer-term efficacy, safety, and tolerability data further support the therapeutic potential of CAB+RPV LA.

Table 1. ATLAS-2M Key Results at Week 48 and Week 96 Analysis Timepoints

| n (%)   | Week 48        |             | Week 96*       |             |
|---|----------------|-------------|----------------|-------------|
|   | Q8W (n=522)    | Q4W (n=523) | Q8W (n=522)    | Q4W (n=523) |
| <b>Primary endpoint (Snapshot based on the ITT-E population)</b><br>HIV-1 RNA $\geq 50$ c/mL (FDA Snapshot) | 9 (1.7)        | 5 (1.0)     | 11 (2.1)       | 6 (1.1)     |
| Adjusted difference (95% CI)  | 0.8 (-0.6–2.2) |             | 1.0 (-0.6–2.5) |             |
| Data in window not $< 50$ c/mL  | 3 (0.6)        | 2 (0.4)     | 2 (0.4)        | 2 (0.4)     |
| Discontinued for lack of efficacy   | 6 (1.1)        | 2 (0.4)     | 8 (1.5)        | 3 (0.6)     |
| Discontinued for other reason while not $< 50$ c/mL   | 0              | 1 (0.2)     | 1 (0.2)        | 1 (0.2)     |
| No virologic data   | 21 (4.0)       | 29 (5.5)    | 36 (6.9)       | 45 (8.6)    |
| Discontinued study due to AE or death   | 9 (1.7)        | 13 (2.5)    | 17 (3.3)       | 17 (3.3)    |
| Discontinued study for other reason   | 12 (2.3)       | 16 (3.1)    | 16 (3.1)       | 27 (5.2)    |
| On study but missing data in window   | 0              | 0           | 3 (0.6)        | 1 (0.2)     |
| <b>Key secondary efficacy endpoint</b><br>HIV-1 RNA $< 50$ c/mL (Snapshot based on the ITT-E population)    | 492 (94.3)     | 489 (93.5)  | 475 (91.0)     | 472 (90.2)  |
| Adjusted* difference (95% CI)   | 0.8 (-2.1–3.7) |             | 0.8 (-2.8–4.3) |             |
| <b>Safety summary (Maintenance Phase)†</b>  |                |             |                |             |
| All AEs   | 473 (90.6)     | 482 (92.2)  | 488 (93.5)     | 499 (95.4)  |
| Grade 2–5 drug-related AEs  | 156 (29.9)     | 164 (31.4)  | 178 (34.1)     | 187 (35.8)  |
| Serious AEs   | 27 (5.2)       | 19 (3.6)    | 33 (6.3)       | 28 (5.4)    |
| AEs leading to discontinuation  | 12 (2.3)       | 13 (2.5)    | 18 (3.4)       | 19 (3.6)    |
| Discontinued for injection-related reason   | 6 (1.1)        | 11 (2.1)    | 7 (1.3)        | 11 (2.1)    |
| Number of ISR events, n (% of injections)   | 2507 (29.6)    | 3152 (20.1) | 3400 (26.5)    | 4157 (17.4) |
| Median ISR duration, days   | 3              | 3           | 3              | 3           |

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.

\*No discontinuations were attributed to COVID-19, though missing virologic data for 4 on-study participants were deemed to be COVID-19 related. COVID-19 introduced negligible impact on efficacy and no impact on the conclusions drawn at Week 96.

†Adjusted for prior exposure to CAB+RPV.

\*Day 1 to Week 100.

#### 402 LONG-ACTING CABOTEGRAVIR+RILPIVIRINE IN OLDER ADULTS: POOLED PHASE 3 WEEK-48 RESULTS

**Paul Benn**<sup>1</sup>, Samia Dakhia<sup>1</sup>, Sterling Wu<sup>2</sup>, Krischan J. Hudson<sup>3</sup>, Yuanyuan Wang<sup>2</sup>, Ronald D'Amico<sup>3</sup>, Vasiliki Chounta<sup>1</sup>, Susan L. Ford<sup>4</sup>, Rodica Van Solingen-Ristea<sup>5</sup>, Simon Vanveggel<sup>5</sup>, Veerle Van Eygen<sup>5</sup>, Joseph W. Polli<sup>3</sup>, Kimberly Smith<sup>3</sup>, William R. Spreen<sup>3</sup>

<sup>1</sup>ViiV Healthcare, Brentford, UK, <sup>2</sup>GlaxoSmithKline, Collegeville, PA, USA, <sup>3</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>4</sup>GlaxoSmithKline, Research Triangle Park, NC, USA, <sup>5</sup>Janssen, Beerse, Belgium

**Background:** Cabotegravir (CAB) and rilpivirine (RPV) long-acting (LA) dosed intramuscularly every 4 weeks (Q4W) was noninferior to daily oral standard of care (SoC) in the ATLAS (NCT02951052) and FLAIR (NCT02938520) Phase 3 studies. CAB+RPV LA dosed every 8 weeks (Q8W) was noninferior to Q4W dosing in the Phase 3b ATLAS-2M study (NCT03299049). Owing to the benefits of ART, there is an increasing proportion of people living with HIV (PLWH) aged  $\geq 50$ y. Efficacy, safety, adherence, and treatment satisfaction outcomes stratified by age ( $\geq 50$ y and  $< 50$ y) across the ATLAS, FLAIR, and ATLAS-2M studies at Week (W) 48 are reported.

**Methods:** Pooled data from the three studies were stratified by age ( $\geq 50$ y and  $< 50$ y). For participants in ATLAS-2M who transitioned from ATLAS LA therapy, only data from ATLAS were included. W48 primary and secondary efficacy endpoints were the proportion of participants with plasma HIV-1 RNA  $\geq 50$  c/mL (virologic nonresponse) and HIV-1 RNA  $< 50$  c/mL (virologic suppression), respectively (FDA Snapshot, intention-to-treat exposed). Adherence, safety, incidence of confirmed virologic failure (CVF; two consecutive measurements of  $\geq 200$  c/mL), and treatment satisfaction (as measured by HIVTSQs) at W48 were secondary endpoints.

**Results:** In total, 399 aged  $\geq 50$ y and 1437 participants aged  $< 50$ y were randomized to either CAB+RPV LA Q8W ( $\geq 50$ y, n=89;  $< 50$ y, n=238), Q4W ( $\geq 50$ y, n=185;  $< 50$ y, n=733), or SoC ( $\geq 50$ y, n=125;  $< 50$ y, n=466). Table 1 shows baseline characteristics and key outcomes. Virologic outcomes were similar across arms and age groups; rates of virologic suppression were high ( $\sim 92$ – $97$ %) and rates of nonresponse were low ( $\sim 2$ %). CVF rates were similarly low across arms and age groups. Safety profiles between participants  $\geq 50$ y and  $< 50$ y were similar for both LA regimens; few adverse events led to withdrawal. Injection site reactions were similar in frequency and severity across LA arms and age groups, with a median duration of 3 days. Mean change (SD) from baseline in total treatment satisfaction was higher in the LA arms vs. SoC but was comparable between age groups (Q8W W48:  $\geq 50$ y, 5.0 [9.18];  $< 50$ y, 4.8 [9.99]; Q4W W44:  $\geq 50$ y, 5.6 [9.50];  $< 50$ y, 4.0 [9.43]; SoC W44:  $\geq 50$ y, 0.4 [7.36];  $< 50$ y, 0.7 [9.02]).

**Conclusion:** CAB+RPV LA demonstrated similar efficacy, safety, and tolerability between participants aged ≥50y and <50y. Treatment satisfaction improved from baseline with CAB+RPV LA and was comparable by age. These data support the therapeutic potential of CAB+RPV LA in older PLWH.

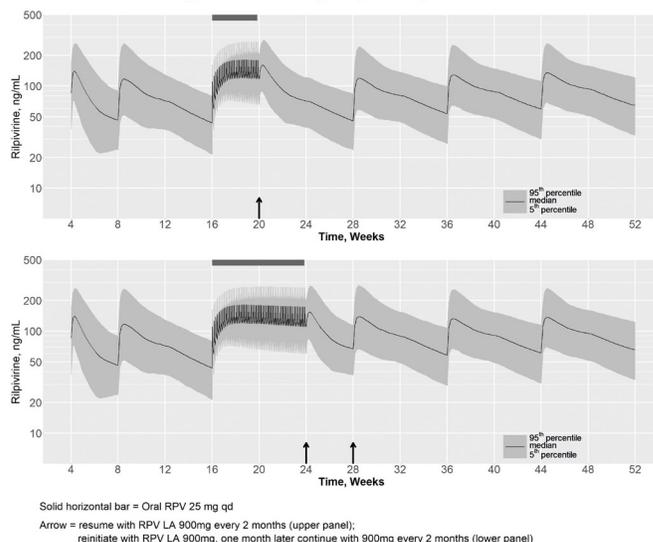
Table 1. Pooled Outcomes From ATLAS, FLAIR, and ATLAS-2M Stratified by Age (<50y and ≥50y)

|  | CAB + RPV LA Q8W |                   | CAB + RPV LA Q4W  |                   | Oral SoC          |                   |
|--|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|  | n (%)            |                   | n (%)             |                   | n (%)             |                   |
|  | ≥50y<br>n=88 (%) | <50y<br>n=238 (%) | ≥50y<br>n=185 (%) | <50y<br>n=733 (%) | ≥50y<br>n=125 (%) | <50y<br>n=486 (%) |
| Gender                                     |                  |                   |                   |                   |                   |                   |
| Male                                       | 65 (73)          | 189 (79)          | 121 (65)          | 560 (76)          | 77 (62)           | 346 (74)          |
| Female                                     | 24 (27)          | 49 (21)           | 64 (35)           | 173 (24)          | 48 (38)           | 120 (26)          |
| Body mass index ≥30 kg/m <sup>2</sup>      | 18 (18)          | 43 (18)           | 37 (20)           | 115 (16)          | 30 (24)           | 73 (16)           |
| Race                                       |                  |                   |                   |                   |                   |                   |
| White                                      | 69 (78)          | 169 (71)          | 140 (76)          | 546 (74)          | 89 (71)           | 319 (68)          |
| Comorbidities at baseline                  |                  |                   |                   |                   |                   |                   |
| 0  | 12 (13)          | 70 (29)           | 28 (15)           | 221 (30)          | 21 (17)           | 183 (39)          |
| 1-2  | 33 (37)          | 81 (34)           | 54 (29)           | 290 (40)          | 37 (30)           | 159 (34)          |
| ≥3   | 44 (49)          | 87 (37)           | 103 (56)          | 222 (30)          | 67 (54)           | 124 (27)          |
| Co-medications at baseline                 |                  |                   |                   |                   |                   |                   |
| 0  | 22 (25)          | 96 (40)           | 26 (14)           | 225 (31)          | 9 (7)             | 136 (29)          |
| 1-2  | 30 (34)          | 82 (34)           | 64 (35)           | 290 (40)          | 35 (28)           | 186 (40)          |
| ≥3   | 37 (42)          | 60 (25)           | 95 (51)           | 218 (30)          | 81 (65)           | 144 (31)          |
| HIV-1 RNA ≥50 c/mL at Week 48*             | 0                | 5 (2.1)           | 4 (2.2)           | 12 (1.6)          | 2 (1.6)           | 8 (1.7)           |
| HIV-1 RNA <50 c/mL at Week 48*             | 86 (96.6)        | 220 (92.4)        | 171 (92.4)        | 679 (92.6)        | 120 (96.0)        | 438 (94.0)        |
| CVF†                                       | 0                | 5 (2.1)           | 2 (1.1)           | 7 (1.0)           | 1 (0.8)           | 6 (1.3)           |
| Any adverse event                          | 81 (91)          | 222 (93)          | 176 (95)          | 652 (94)          | 99 (79)           | 367 (79)          |
| Drug related                               | 69 (78)          | 203 (85)          | 155 (84)          | 606 (83)          | 11 (9)            | 85 (18)           |
| Adverse event leading to withdrawal        | 4 (4)            | 5 (2)             | 7 (4)             | 25 (3)            | 3 (2)             | 6 (1)             |
| Drug related                               | 3 (3)            | 3 (1)             | 6 (3)             | 14 (2)            | 0                 | 4 (1)             |
| Any serious adverse event                  | 6 (7)            | 9 (4)             | 7 (4)             | 30 (4)            | 4 (3)             | 25 (5)            |
| Drug related                               | 0                | 1 (<1)            | 1 (<1)            | 1 (<1)            | 0                 | 1 (<1)            |
| Number of injections                       | 1456             | 3754              | 4456              | 17,204            |                   |                   |
| Number of ISR events                       | 431 (30)         | 1259 (34)         | 2285 (51)         | 13,237 (77)       |                   |                   |
| Grade 1 events - mild                      | 390 (25)         | 948 (25)          | 1866 (42)         | 10,885 (63)       |                   |                   |
| Grade 2 events - moderate                  | 68 (5)           | 285 (8)           | 396 (9)           | 2193 (13)         |                   |                   |
| Grade 3 events - severe                    | 3 (<1)           | 26 (<1)           | 23 (<1)           | 155 (<1)          |                   |                   |
| ISR duration ≤7 days                       | 373 (87)         | 1121 (89)         | 1945 (85)         | 11,646 (88)       |                   |                   |
| Participants withdrawing due to ISRs       | 2 (2)            | 2 (<1)            | 3 (2)             | 6 (<1)            |                   |                   |
| Injections received outside ±7-day window‡ | 10 (2)           | 22 (2)            | 74 (2)            | 258 (2)           |                   |                   |

CAB, cabotegravir; CVF, confirmed virologic failure; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SoC, standard of care.  
 \*FDA Snapshot algorithm. Percentage derived from the total number of participants assessed at Week 48.  
 †Two consecutive measurements of HIV-1 RNA ≥200 c/mL.  
 ‡Four ISRs were not applicable for grading.  
 §Percentage calculated relative to the number of injection visits.

(Injection 3 or later): re-initiate with 900mg dose (3mL) followed by a second 900mg dose (3mL) one month later, then continue Q2M dosing.  
**Conclusion:** Adherence to the Q2M RPV LA injection schedule is strongly recommended. Oral therapy to cover planned dosing interruptions of RPV LA injections can provide exposures within ranges observed in clinical studies. Recommendations for managing dosing interruptions are aligned for RPV LA and CAB LA, to facilitate dosing for the complete regimen.

Figure 1: Simulated RPV Plasma Concentration-Time Profiles of Bridging With Oral RPV 25 mg qd During Planned RPV LA Dosing Interruptions for 1 Month (And Resuming With RPV LA 900 mg Every 2 Months; Upper Panel) and 2 Months (Re-initiating with RPV LA 900 mg, 1 Month Later Another RPV LA 900 mg, Then RPV LA 900 mg Every 2 Months)



Solid horizontal bar = Oral RPV 25 mg qd  
 Arrow = resume with RPV LA 900mg every 2 months (upper panel);  
 reinitiate with RPV LA 900mg, one month later continue with 900mg every 2 months (lower panel)

**403 POPPK MODELING OF Q2M IM RPV LA FOR MANAGING DOSING INTERRUPTIONS IN HIV-1 PATIENTS**

Stefaan Rossenu<sup>1</sup>, Martine Neyens<sup>1</sup>, Rodica Van Solingen-Ristea<sup>1</sup>, Bryan Baugh<sup>2</sup>, Herta Crauwels<sup>1</sup>

<sup>1</sup>Janssen, Beerse, Belgium, <sup>2</sup>Janssen Pharmaceutical, Research and Development, Titusville, FL

**Background:** Long-acting rilpivirine (RPV LA) is intended for coadministration with cabotegravir long-acting (CAB LA) as a complete 2-drug injectable regimen for HIV-1 treatment. Eight-weekly RPV LA plus CAB LA was noninferior to 4-weekly RPV LA plus CAB LA in maintaining HIV-1 suppression (ATLAS-2M; Overton TE et al. CROI 2020 Abstract 34).

**Methods:** Every 2 months (Q2M) RPV LA consists of 1-month oral RPV 25mg once daily for tolerability assessment, two initiation RPV LA 900mg (3mL) intramuscular (IM) doses separated by 1 month and subsequent 900mg doses Q2M, to be administered with the Q2M CAB regimen. Population pharmacokinetic (PopPK) modeling and simulation was used to inform strategies for managing dosing interruptions, aimed at minimizing impact on the overall RPV LA PK profile. Simulations included effects on RPV concentrations of Q2M vs 8-weekly dosing, IM dosing delays, and bridging with oral RPV to cover a planned missed IM injection. Simulated RPV concentrations were compared to the 5th percentile of observed RPV concentrations 4 weeks after the initial RPV LA 900mg dose in ATLAS/FLAIR and to concentrations observed in the oral RPV development program, as done for monthly RPV LA (Rossenu S et al. AIDS 2020 PEB0264).

**Results:** Q2M vs 8-weekly dosing, with a 7-day window, has minimal impact on overall RPV PK profile. IM dosing delays of >7 days may have a larger impact, particularly in the first few months of therapy. If a patient plans to miss a scheduled injection by >7 days, oral RPV can provide coverage of up to 1 missed injection (Figure 1). Recommendations for resuming RPV LA after missed injections are: If time since last injection: - ≤2 months (Injection 2) or ≤3 months (Injection 3 or later): continue with 900mg dose (3mL) as soon as possible, then continue Q2M dosing. - >2 months (Injection 2) or >3 months

**404 BICTEGRAVIR AND CABOTEGRAVIR: IN VITRO PHENOTYPIC SUSCEPTIBILITY OF HIV-1 NONGROUP M**

Charlène Martin<sup>1</sup>, Ségolène Gracias<sup>1</sup>, Charlotte Charpentier<sup>2</sup>, Diane Descamps<sup>2</sup>, Quentin Le Hingrat<sup>3</sup>, Jean-Christophe Plantier<sup>1</sup>, Elodie Alessandri-Gradt<sup>1</sup>  
<sup>1</sup>Rouen University Hospital, Rouen, France, <sup>2</sup>Hôpital Bichat-Claude-Bernard, Paris, France, <sup>3</sup>University Paris Diderot, Paris, France

**Background:** HIV-1 are classified into 4 groups: M (pandemic), O (endemic in Cameroon), N and P (more rare). The WHO has recommended the use of integrase strand transfer inhibitors (INSTI) as first line treatment. Previous phenotypic studies showed the susceptibility of HIV-1/non-M to raltegravir and dolutegravir and a more variable susceptibility to elvitegravir, in association with a probable specific genotypic pattern. This study was conducted to evaluate the phenotypic susceptibility of a large panel of HIV-1/non-M to the newest INSTIs, bictegravir (BIC) and cabotegravir (CAB), which are promising molecules regarding the limited therapeutic arsenal available for HIV-1/O infected patients.

**Methods:** 44 clinical isolates of HIV-1/non-M (41 O, 2 N and 1 P) were tested and 5 isolates of HIV-1/M from cell culture were used as standard references. The phenotypic assay was performed by infecting fresh PBMCs with non-M supernatants for 2 hours and adding 5 increasing concentrations of the drug (0.1 – 1000 nM) in quadruplicates for 3 days. The viral material was quantified (qRT-PCR) for the different conditions and inhibitory concentrations 50% (IC<sub>50</sub>) were calculated for each isolate. The Fold Change (FC) expressed the ratio between the IC<sub>50</sub> of the tested strain and the mean IC<sub>50</sub> of HIV-1/M.

**Results:** HIV-1/M reference strains showed a mean IC<sub>50</sub> of 1.86 and 5.24 nM for BIC and CAB respectively. Mean IC<sub>50</sub> (min ; max) of HIV-1/O were 2.24 nM (0.03 ; 9.47) and 4.94 nM (0.04 ; 15.64) for BIC and CAB respectively. FC values ranged from 0.01 to 5.09, with 17 isolates showing an FC>1 both for BIC and CAB. HIV-1/N showed a mean IC<sub>50</sub> of 1.29 and 3.95 nM for BIC and CAB respectively, versus 0.81 and 4.26 nM for the HIV-1/P isolate. No significant difference between means of HIV-1/M and HIV-1/non-M was observed for the two drugs.

**Conclusion:** Our results confirm the susceptibility of HIV-1/non-M to the new INSTIs BIC and CAB but with a higher variability of IC<sub>50</sub> for CAB (maximum of 15.62 versus 9.44 for BIC). Similar observations were obtained for the HIV-1/M clinical isolates. These data reflect the need for careful monitoring of the dosage especially with injectable CAB in patients. Clinical studies of in vivo efficacy are still required to confirm these promising phenotypic results.

**405 IMPACT OF ANTIRETROVIRAL REGIMENS ON MORTALITY IN PATIENTS WITH ADVANCED HIV DISEASE**

Joaquin Burgos-Cibrian<sup>1</sup>, Sergio Moreno Fornés<sup>2</sup>, Juliana Reyes-Urueña<sup>2</sup>, Andreu Bruguera<sup>2</sup>, Berta Raventós<sup>3</sup>, Josep Maria Llibre<sup>4</sup>, Arkaitz Imaz<sup>2</sup>, Pere Domingo<sup>6</sup>, Emili Letang<sup>7</sup>, Joaquin Peraire<sup>8</sup>, Joaquin-Amat Orti<sup>9</sup>, David Dalmau<sup>10</sup>, Jordi Casanova<sup>2</sup>, Jose M. Miro<sup>11</sup>, Vicenç Falcó<sup>1</sup>, for the PISCIS Investigators

<sup>1</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, <sup>2</sup>Centre d'Estudis Epidemiològics Sobre les ITS i Sida de Catalunya, Barcelona, Spain, <sup>3</sup>Vall d'Hebron Research Institute, Barcelona, Spain, <sup>4</sup>Hospital Germans Trias i Pujol, Barcelona, Spain, <sup>5</sup>Bellvitge University Hospital, Barcelona, Spain, <sup>6</sup>Hospital Sant Pau, Barcelona, Spain, <sup>7</sup>Hospital del Mar, Barcelona, Spain, <sup>8</sup>Hospital Universitari Joan XXII, Tarragona, Spain, <sup>9</sup>Hospital Verge de la Cinta, Tarragona, Spain, <sup>10</sup>TaiMed Biologics Inc, Taipei City, Taiwan, <sup>11</sup>Hospital Clinic of Barcelona, Barcelona, Spain

**Background:** Scarce data exist regarding the efficacy of antiretroviral (ARV) treatment in patients with advanced HIV disease. The aim of the study was to assess the impact of ARV regimens on the clinical outcomes among naïve patients with advanced HIV presentation in real life settings.

**Methods:** A multicentre, population-based, prospective cohort study was performed. Treatment-naïve subjects with advanced HIV diseases (CD4+T cell count < 200 cells/ml or presence of an AIDS-defining illness) who started therapy between 2010 and 2018, from 18 hospitals in Spain, were included. The primary outcome was the rate of mortality at three years. Secondary outcomes included discontinuation or change of ARV regimen, virological effectiveness (viral load of ≤ 200 copies/ml) and immune reconstitution (achieve CD4+T cell count > 350 cells/ml). Kaplan-Meier curves and long-rank test were used to analyse different outcomes. A Cox proportional hazard model was performed to identify predictors of death

**Results:** A total of 1170 naïve patients with advanced HIV disease started ARV treatment: 44.9% with PIs based regimen, 29.6% with NNRTIs and 25.6% with InSTI. The most frequently third-drug was darunavir (73%), efavirenz (70.9%) and dolutegravir (47%), respectively. The median follow-up was 5 years (5695 person-years), median CD4+T cell count at baseline was 101 cells/ml and 30.3% had an AIDS-defining illness. Crude mortality rate at three years of follow-up was 6.1% (95% CI, 4.1-8.1) for PI based regimen, 4% (95% CI, 1.8-6.2) for NNRTI and 2.6% (95% CI, 0.9-4.3) for InSTI. In patients with an AIDS-defining illness, mortality rate was 14.6% (95% CI, 7.2-21.4) for PI, 9.1% (95% CI, 2.4-7) for NNRTI and 5.8% (95% CI, 1.0-11.4) for InSTI. Factors associated with mortality were higher age and AIDS-defining illness at inclusion, whilst treatment with InSTI regimen had a trend as protective factor (HR 0.53, 95% CI, 0.25-1.14). Patients who started with InSTI based regimen achieved viral suppression and immune reconstitution earlier (0.2 and 0.3 years, respectively), than those with PI and NNRTI based regimens, (1.1 and 1.4; 0.3 and 0.9, respectively). Over the follow-up period, 56.8% of patients with PI regimen, 53.9% with NNRTI and 13.6% with InSTI changed treatment.

**Conclusion:** In this large real-life cohort study, a lower mortality and a less rate of discontinuation in patients treated with InSTIs regimens were observed among naïve patients with advance HIV disease.

Cumulative probability of progression to mortality, virological effectiveness and immune restoration by compared the three ART regimens on-treatment

| Endpoint                                   | 1-year cumulative rate (95% CI) | 2-year cumulative rate (95% CI) | 3-year cumulative rate (95% CI) |
|--|---------------------------------|---------------------------------|---------------------------------|
| Mortality                                  | PI: 4.6 (2.8; 6.4)              | PI: 5.1 (3.2; 7.0)              | PI: 6.1 (4.1; 8.1)              |
|  | NNRTI: 1.3 (0.0; 2.6)           | NNRTI: 2.3 (0.6; 4.1)           | NNRTI: 4.0 (1.8; 6.2)           |
|  | InSTI: 2.0 (0.3; 3.5)           | InSTI: 2.3 (0.7; 3.9)           | InSTI: 2.6 (0.9; 4.3)           |
| Virological effectiveness (≤200 copies/ml) | PI: 92.7 (89.9; 94.7)           | PI: 96.2 (93.9; 97.6)           | PI: 97.9 (95.9; 98.9)           |
|  | NNRTI: 92.0 (88.1; 94.68)       | NNRTI: 94.8 (91.3; 96.9)        | NNRTI: 97.6 (94.3; 98.9)        |
|  | InSTI: 98.0 (95.6; 99.1)        | InSTI: 99.2 (96.9; 99.8)        | InSTI: 100.0 (97.2; 100.0)      |
| Immune restoration (> 350 CD4/ml)          | PI: 30.9 (26.6; 34.9)           | PI: 33.5 (28.6; 38.0)           | PI: 35.9 (31.0; 40.2)           |
|  | NNRTI: 42.8 (36.7; 48.3)        | NNRTI: 48.3 (43.9; 52.7)        | NNRTI: 53.4 (47.4; 59.4)        |
|  | InSTI: 43.9 (38.0; 49.2)        | InSTI: 46.6 (40.3; 52.8)        | InSTI: 48.9 (42.7; 55.1)        |

InSTI: integrase strand transfer inhibitors. NNRTI: nonnucleoside reverse transcriptase inhibitors. PI: protease inhibitors. 95% CI (Confidence interval of 95%)

**406 EFFECTIVENESS OF RECOMMENDED 3-DRUG REGIMENS FOR TREATING ADVANCED HIV INFECTION**

Karam Mounzer<sup>1</sup>, Laurence Brunet<sup>2</sup>, Jennifer S. Fusco<sup>2</sup>, Ian McNicholl<sup>3</sup>, Helena Diaz-Cuervo<sup>2</sup>, Michael Sension<sup>4</sup>, Lewis McCurdy<sup>5</sup>, Gregory P. Fusco<sup>2</sup>

<sup>1</sup>Philadelphia FIGHT, Philadelphia, PA, USA, <sup>2</sup>Epididian, Durham, NC, USA, <sup>3</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>4</sup>CAN Community Health, Fort Lauderdale, FL, USA, <sup>5</sup>Atrium Health, Charlotte, NC, USA

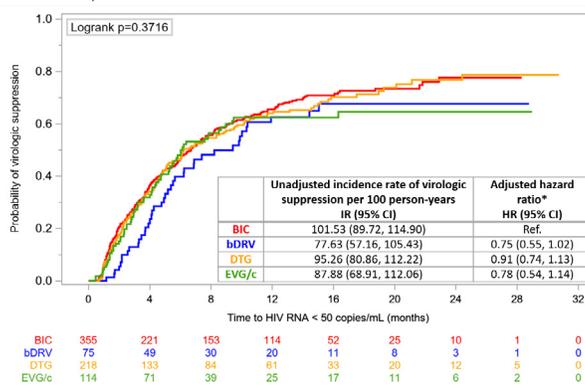
**Background:** There is limited evidence on regimen options for people living with HIV (PLWH) initiating antiretroviral therapy (ART) with advanced infection. The effectiveness of one of the newest 3-drug regimen (3DR), bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), was therefore compared to other 3DRs that included boosted darunavir (bDRV), dolutegravir (DTG) or elvitegravir/cobicistat (EVG/c) among ART-naïve PLWH with CD4 count <200 cells/μL.

**Methods:** ART-naïve adults with advanced HIV-1 infection (CD4 count <200 cells/μL) initiating B/F/TAF or a bDRV, DTG or EVG/c-based 3DR between 01JAN2018 and 31JUL2019 in the OPERA Cohort were included. Regimen discontinuation and virologic suppression to <50 copies/mL were assessed with Kaplan-Meier methods and unadjusted Poisson regression. The association between regimen and virologic suppression was assessed with a Cox proportional hazards model with inverse probability of treatment weighting (Figure).

**Results:** Overall, 961 PLWH initiated ART with advanced HIV infection: 416 B/F/TAF (age ≤25: 10%, CD4 ≤50 cells/μL: 36%), 106 bDRV (age ≤25: 19%, CD4 ≤50: 33%), 271 DTG (age ≤25: 13%, CD4 ≤50: 30%), 168 EVG/c (age ≤25: 14%, CD4 ≤50: 38%). In unadjusted analyses, B/F/TAF initiators were statistically significantly less likely to discontinue their regimen (incidence rate per 100 person-years [IR]: 12.54; 95% confidence interval [CI]: 9.94, 15.83) compared to other regimens (range IR: 21.40 to 35.27). While 70% reached a CD4 count ≥200 cells/μL overall, CD4:CD8 ratio normalization (≥1) was achieved by <7% and did not differ across regimens (logrank p=0.52). Incident immune reconstitution inflammatory syndrome (IRIS) was rare (3 B/F/TAF, 1 bDRV, 2 DTG, 0 EVG/c). Follow-up viral loads were available for 762 PLWH (355 B/F/TAF, 75 bDRV, 218 DTG, 114 EVG/c). Baseline characteristics were well balanced with inverse probability of treatment weights. Compared to B/F/TAF, bDRV initiators were numerically less likely to achieve virologic suppression (adjusted hazard ratio: 0.75; 95% CI: 0.55, 1.02). No statistically significant difference in the likelihood of virologic suppression was detected between B/F/TAF and DTG or EVG/c 3DRs (Figure).

**Conclusion:** Among PLWH with advanced HIV infection initiating ART, those on B/F/TAF appeared less likely to discontinue their regimen compared to other 3DRs (unadjusted) and were numerically more likely to achieve virologic suppression compared to bDRV but did not differ from those on DTG or EVG/c-based 3DR (adjusted).

Figure. Virologic suppression (viral load < 50 copies/mL) over follow-up: cumulative probabilities (Kaplan-Meier), incidence rates (Poisson regression), and adjusted\* association with regimen (Cox proportional hazard marginal structural model)



\*Marginal structural model with stabilized inverse probability of treatment weights controlling for baseline index year, age, CD4 cell count, viral load, sex, race, HBV

#### 407 BLIP INCIDENCE IN DOLUTEGRAVIR- OR EFVIRENZ-BASED ART DURING ACUTE HIV INFECTION

**Bharat Nandakumar**<sup>1</sup>, Carlo Sacdalan<sup>1</sup>, Suteeraporn Pinyakorn<sup>2</sup>, Eugene Kroon<sup>1</sup>, Trevor A. Crowell<sup>3</sup>, Donn J. Colby<sup>2</sup>, Somchai Sreepleanjan<sup>1</sup>, Peeriya Prueksakaew<sup>1</sup>, Nitiya Chomchey<sup>1</sup>, Denise C. Hsu<sup>2</sup>, Sandhya Vasan<sup>1</sup>, Nittaya Phanuphak<sup>1</sup>

<sup>1</sup>SEARCH, Bangkok, Thailand, <sup>2</sup>Henry M Jackson Foundation, Bethesda, MD, USA

**Background:** Transient viral blips are observed in up to 50% of persons living with HIV on ART. As first-line regimens shift from efavirenz (EFV) to dolutegravir (DTG), evaluation of blip incidence is needed. We compared blip incidence in participants diagnosed and started on either regimen during acute HIV infection (AHI) in Bangkok, Thailand.

**Methods:** From 2013-2018, participants with AHI in SEARCH010/RV254 cohort initiated EFV- or DTG-based regimens. Fiebig stage was assessed at enrolment using nucleic acid testing and sequential immunoassays. HIV RNA was measured at enrolment, weeks 2, 4, 8, 12 and every 12 weeks thereafter. Blip was defined as a transiently detectable RNA ( $\geq 20$  c/mL) bookended by undetectable measurements with self-reported adherence of  $>95\%$ . Blips were categorised as "low" (20-50 c/mL), "medium" (51-200 c/mL) or "high" ( $>200$  c/mL). Blips were counted after achieving viral suppression with 2 consecutive undetectable RNA measurements.

**Results:** A total of 324 participants were analysed, predominantly MSM (98.5%) with a median age of 26 (IQR 22-31) years. Of these, 280 started EFV and 44 started DTG-based ART. Fifty-five blips were observed with an incidence of 11.5 (95% CI: 8.7-15.7) per 100 person-years. Blip incidence was not statistically different between DTG and EFV group (15.5 vs 10.8,  $p=0.265$ ). The frequency of blip in DTG and EFV were 11 vs 44 ( $p=0.041$ ). The categories respectively were 6 (55%) vs 37 (84%) in low, 4 (36%) vs 7 (16%) in medium and 1 (9%) vs 0 in high. Blip range was 21-398 c/mL (DTG) and 21-160 c/mL (EFV), while blip median was 34 (IQR 24-103) and 30 (IQR 24-43) respectively ( $p=0.215$ ). The median time from ART initiation to viral suppressions was 8 weeks (IQR 6-12) on DTG and 23 weeks (IQR 12-24) on EFV ( $p<0.001$ ). The median time from ART initiation to first blip was 72 weeks in both groups. In the multivariate model, factors associated with higher incidence rate of blips are baseline HIV RNA  $>6\log_{10}$  c/mL and diagnosis at Fiebig stages III-V. CD4 count and ART regimen (EFV or DTG) were not associated with blip incidence rate ratio.

**Conclusion:** There is a non-significant trend of increasing frequency and magnitude of blips in DTG compared to EFV regimen. Time to viral suppression was faster with DTG and may have led to a longer time-at-risk for blips. Magnitude of blips in both regimens was low, suggesting a low risk of subsequent viral failure. Participants with baseline HIV RNA  $>100,000$  c/mL and Fiebig stages III-V at enrolment were predictive of blips.

#### 408 HMMCGAG ASSAY DETECTS HIGH VIREMIA RATES ON ART STARTED DURING ACUTE HIV INFECTION

**Donn J. Colby**<sup>1</sup>, Suteeraporn Pinyakorn<sup>1</sup>, Carlo Sacdalan<sup>2</sup>, Adam Yates<sup>1</sup>, Eugene Kroon<sup>2</sup>, Denise C. Hsu<sup>3</sup>, Nittaya Phanuphak<sup>2</sup>, Jintanat Ananworanich<sup>4</sup>, Jeffry Lifson<sup>5</sup>, Brandie Fullmer<sup>5</sup>, Jorden L. Welker<sup>5</sup>, Robert Gorelick<sup>5</sup>, Sandhya Vasan<sup>1</sup>, Frank Maldarelli<sup>6</sup>, for the RV254/SEARCH010 Research Group

<sup>1</sup>US Military HIV Research Program, Bethesda, MD, USA, <sup>2</sup>Institute of HIV Research and Innovation, Bangkok, Thailand, <sup>3</sup>Armed Forces Research Institute of Medical Sciences in Bangkok, Bangkok, Thailand, <sup>4</sup>University of Amsterdam, Amsterdam, Netherlands, <sup>5</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA, <sup>6</sup>National Cancer Institute, Bethesda, MD, USA

**Background:** The goal of antiretroviral therapy (ART) for HIV infection is to suppress the plasma viral load (VL) to below the limit of detection (LOD) on commercial assays, thereby preventing adverse effects of HIV viremia. However, ultrasensitive assays, with LOD  $<0.3$  copies/mL, can detect residual viremia in most chronically infected individuals despite many years of suppressive ART, reflecting HIV production from long lived reservoirs. Levels of residual viremia in those initiating ART during acute HIV infection (AHI) are not known.

**Methods:** The RV254/SEARCH010 cohort has recruited participants with AHI in Bangkok, Thailand since 2009. Participants who started ART immediately at study entry, with VL  $<50$  copies/mL at 24 and 48 weeks were included in the analysis. The HMMCGag single copy HIV-1 qRT-PCR assay was used for the plasma viral load analyses. This assay detects a relatively conserved target directly upstream of gag (Somsouk, PLoS One, 2014) and detects clades A through G.

**Results:** Participants ( $n=419$ ) had median age 26 (interquartile range (IQR) 23-31) and were 98% male. At HIV diagnosis median (IQR) CD4 was 364 (266 -

490) cells/mm<sup>3</sup>, CD8 was 510 (335 - 857) cells/mm<sup>3</sup>, and the CD4/CD8 ratio was 0.71 (0.44-1.04). HIV subtypes were 76.9% CRF01\_AE and 11.2% recombinant CRF01\_AE/B. Initial ART regimens were efavirenz-based in 73.0% and contained an integrase inhibitor in 26.5%. Baseline median (IQR) VL was 5.94 (5.23-6.78) log<sub>10</sub> copies/mL in the commercial assay and 5.83 (5.06-6.54) log<sub>10</sub> copies/mL in the HMMCGag assay, with high correlation ( $r=0.92$ ,  $p<0.001$ ). Although all participants had VL 6.0 log<sub>10</sub> copies/mL, and time to VL suppression on ART  $>16$  weeks (Table). Age, HIV subtype, CD4, CD8, CD4/CD8 ratio, and ART regimen were not associated with viremia.

**Conclusion:** Despite all participants having undetectable VL on the commercial assay, the majority had residual viremia on the HMMCGag assay, indicating persistence of a virus production through at least 48 weeks. Further studies are needed to determine the source and durability of this reservoir in participants who start ART during AHI.

Table: Detectable HMMCGag at either week 24 or 48, by significant characteristics. All VL  $<$  LOD by commercial assay.

|  | N   | Detectable viremia at either week 24 or week 48, n(%) | aOR  | 95% CI     | p-value  |
|--|-----|---|------|------------|----------|
| <b>Fiebig stage</b>                            |     |   |      |            |          |
| Fiebig I                                       | 44  | 13 (29.6)   | ref. |            |          |
| Fiebig II                                      | 77  | 64 (83.1)   | 2.21 | 1.35-3.60  | 0.002    |
| Fiebig III                                     | 118 | 103 (87.3)  | 3.69 | 2.23-6.09  | $<0.001$ |
| Fiebig IV-V                                    | 53  | 52 (98.1)   | 6.36 | 3.38-11.94 | $<0.001$ |
| <b>Pre-ART VL</b>                              |     |   |      |            |          |
| $\leq 6 \log_{10}$ copies/mL                   | 161 | 110 (68.3)  | ref. |            |          |
| $> 6 \log_{10}$ copies/mL                      | 131 | 122 (93.1)  | 2.44 | 1.60-3.72  | $<0.001$ |
| <b>Time to VL <math>&lt;</math> LOD on ART</b> |     |   |      |            |          |
| $\leq 16$ weeks                                | 179 | 124 (69.3)  | ref. |            |          |
| $> 16$ weeks                                   | 113 | 108 (95.6)  | 1.83 | 1.22-2.75  | 0.003    |

#### 409 CURRENT ANTIRETROVIRAL TREATMENT AMONG PEOPLE WITH HIV IN CARE IN THE US (2018-2019)

**Jimmy Ma**<sup>1</sup>, Robin M. Nance<sup>1</sup>, Joseph A. Delaney<sup>2</sup>, Bridget M. Whitney<sup>1</sup>, Sonia Napravnik<sup>3</sup>, Kenneth H. Mayer<sup>4</sup>, Richard Moore<sup>5</sup>, Katerina Christopoulos<sup>6</sup>, Ronnie M. Gravett<sup>7</sup>, Laura Bamford<sup>8</sup>, Barbara Gripshover<sup>9</sup>, Michael Saag<sup>7</sup>, Heidi Crane<sup>1</sup>, Mari M. Kitahata<sup>1</sup>, for the CNICS Cohort

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>University of Manitoba, Winnipeg, Canada, <sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>4</sup>Fenway Health, Boston, MA, USA, <sup>5</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>6</sup>University of California San Francisco, San Francisco, CA, USA, <sup>7</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>8</sup>University of California San Diego, San Diego, CA, USA, <sup>9</sup>Case Western Reserve University, Cleveland, OH, USA

**Background:** Newer antiretroviral drugs and dosing formulations have expanded treatment options for people with HIV (PWH) in recent years. In a previous study, we found that the prevalence of PWH with limited antiretroviral treatment (ART) options declined dramatically to  $<2\%$  after the introduction of the integrase strand transfer inhibitor (INSTI) class. Newer INSTIs, including dolutegravir (DTG) and bictegravir (BIC), have improved viral suppression and become the recommended "core" components in initial ART regimens. However, information regarding the uptake of newer drugs and current ART use patterns is lacking.

**Methods:** We studied all PWH aged 18 or older in routine clinical care 01/2018-12/2019 across the US in the CFAR Network of Integrated Clinical Systems (CNICS) cohort. We examined current ART use, defined as the most recent multi-drug ART regimen, by core class (INSTI, non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI)), and by individual drugs in the overall cohort and among ART-naïve PWH initiating ART 2018-2019.

**Results:** Among 14,727 PWH in care, 96% were on ART, median age was 51 years, 20% were female, 61% non-white, and 55% men who had sex with men as a risk factor for HIV. Among PWH on ART, the majority were receiving INSTI-based regimens (72%) of which 39% were anchored by BIC and 37% by DTG. A small proportion of PWH were on PI- (7%) and NNRTI- (9%) based regimens which on average were started 4 years prior to the study period (2014), with NNRTI use limited to single-tablet regimens (STRs, 99%). Sixty-nine percent of all regimens included tenofovir alafenamide (TAF) while only 10% used tenofovir disoproxil fumarate (TDF). Among 458 ART-naïve PWH initiating treatment in 2018-2019, 93% were on INSTI-based regimens of which 73% were anchored by BIC and 23% by DTG.

**Conclusion:** The results of this study suggest high current uptake of ART nationally among PWH in care, predominance of newer INSTI-based regimens, and the emergence of BIC/TAF/FTC as the preferred regimen for both ART-experienced and naïve individuals initiating ART. Few PWH remain on core agents with a lower barrier to resistance formulated as STRs. In addition, TAF

has replaced TDF as the preferred form of tenofovir across all regimens. Further study of ART utilization patterns among specific subgroups of PWH is needed to guide development of targeted approaches to improve uptake and clinical outcomes for all PWH as the ART landscape continues to evolve rapidly.

Table 1. Current ART usage among persons with HIV in routine care

| Antiretroviral Medications            | Overall (n = 14169) | Overall Median Start Year (IQR) | First ART Initiated 01/2018-12/2019 (n = 458) |
|---------------------------------------|---------------------|---------------------------------|---|
| <b>INSTI-based regimen*</b>           | 10177 (72%)         | 2018 (2016-2019)                | 425 (93%)                                     |
| BIC/TAF/FTC (Biktarvy)                | 3987 (39%)          | 2019 (2018-2019)                | 309 (73%)                                     |
| Dolutegravir                          | 3776 (37%)          | 2016 (2015-2018)                | 96 (23%)                                      |
| EVG/c/TAF/FTC (Genvoya)               | 2021 (20%)          | 2016 (2015-2017)                | 16 (4%)                                       |
| EVG/c/TDF/FTC (Stribild)              | 204 (2%)            | 2015 (2014-2016)                | 0 (0%)  |
| Raltegravir                           | 224 (2%)            | 2014 (2011-2017)                | 5 (1%)  |
| <b>PI-based regimen*</b>              | 990 (7%)            | 2014 (2011-2017)                | 8 (2%)  |
| Darunavir                             | 833 (84%)           | 2015 (2012-2017)                | 7 (88%)                                       |
| Atazanavir                            | 150 (15%)           | 2012 (2006-2017)                | 1 (13%)                                       |
| <b>NNRTI-based regimen*</b>           | 1333 (9%)           | 2014 (2012-2017)                | 10 (2%)                                       |
| Doravirine                            | 14 (1%)             | 2019 (2019-2019)                | 2 (20%)                                       |
| RPV/TAF/FTC (Odefsey)                 | 846 (63%)           | 2016 (2014-2017)                | 8 (80%)                                       |
| RPV/TDF/FTC (Complera)                | 103 (8%)            | 2014 (2013-2016)                | 0 (0%)  |
| EFV/TDF/FTC (Atripla)                 | 244 (18%)           | 2009 (2005-2012)                | 0 (0%)  |
| <b>Multi-core regimen**</b>           | 1669 (12%)          | 2017 (2015-2018)                | 15 (3%)                                       |
| INSTI + other core agent              | 1586 (95%)          | 2017 (2015-2018)                | 15 (100%)                                     |
| Dolutegravir + Darunavir <sup>†</sup> | 650 (41%)           | 2017 (2015-2018)                | 7 (47%)                                       |
| <b>NRTI components<sup>‡</sup></b>    |                     |                                 |   |
| Any TAF Use                           | 9737 (69%)          | 2018 (2016-2019)                | 402 (88%)                                     |
| Any ABC Use                           | 2370 (17%)          | 2016 (2015-2017)                | 40 (9%)                                       |
| Any TDF Use                           | 1438 (10%)          | 2015 (2012-2017)                | 5 (1%)  |

**Footnotes:**  
 \*Shaded row percentage is based on the column total sample size. Sub-row percentages are based on the parent shaded row total size. Sub-row percentages may not add up to 100.  
 \*\*Multi-core regimen includes any regimen containing multiple core drugs (INSTI, PI excluding ritonavir/cobicistat, and NNRTI).  
 †Percentage is based on totals in row above.  
 ‡Sub-row percentages are based on the column total sample size and may not add up to 100.  
**Abbreviations:** ABC, abacavir; ART, antiretroviral therapy; EVG/c, elvitegravir with cobicistat; EFV, efavirenz; FTC, emtricitabine; INSTI, integrase strand transferase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

**410 CHARACTERIZING FIRST VIRAL FAILURES AMONG ANTIRETROVIRAL THERAPY INITIATORS IN THE US**

Thibaut Davy-Mendez<sup>1</sup>, Sonia Napravnik<sup>2</sup>, David A. Wohl<sup>2</sup>, Ellen F. Eaton<sup>3</sup>, Richard Moore<sup>4</sup>, Edward R. Cachay<sup>5</sup>, Katerina Christopoulos<sup>1</sup>, George A. Yendewa<sup>6</sup>, Kenneth H. Mayer<sup>7</sup>, Mari M. Kitahata<sup>8</sup>, Joseph J. Eron<sup>2</sup>, for the Centers for AIDS Research Network of Integrated Clinical Systems

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>4</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>5</sup>University of California San Diego, San Diego, CA, USA, <sup>6</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>7</sup>The Fenway Institute, Boston, MA, USA, <sup>8</sup>University of Washington, Seattle, WA, USA

**Background:** Despite antiretroviral therapy (ART) improvements, some persons with HIV continue to experience suboptimal virologic outcomes. We examined reasons for first virologic failure in a large clinical population.

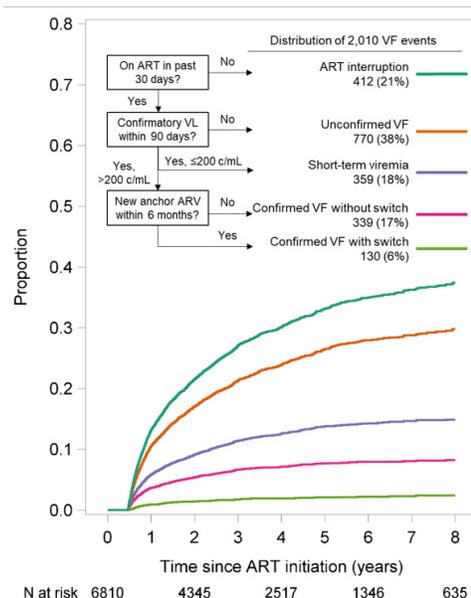
**Methods:** In 7 US clinical cohorts, 2008–2018, we estimated time from ART initiation to virologic failure (VF), defined as the first viral load (VL) >200 copies/mL after 24 weeks of ART. We assigned VF events to 5 exclusive categories according to ART use and subsequent VL (Fig. 1): 1) off ART for >30 days on VF date ("ART interruption"); 2) on ART + no confirmatory VL within 90 days ("unconfirmed VF"); 3) on ART + VL ≤200 within 90 days ("short-term viremia"); 4) on ART + confirmatory VL >200 within 90 days ("confirmed VF without ART switch"); and 5) on ART + confirmatory VL >200 within 90 days + new anchor agent within 6 months ("confirmed VF with ART switch"). We used Aalen-Johansen methods to estimate cumulative incidence curves and Fine-Gray models adjusted for site to compare patient characteristics, treating each outcome and mortality as competing events.

**Results:** Of 6,810 patients (83% men, 40% Black, 40% White, median age 37 years), 37% initiated ART with an NNRTI (81% EFV), 33% an INSTI (51% EVG, 21% DTG), and 21% a boosted PI (49% DRV, 43% ATV), all in combination with 2 NRTIs. The overall VF risk was 21.5% by 2 years post-ART initiation (Fig. 1, top line). By 8 years post-initiation, 14.9% of patients experienced unconfirmed VF, 7.6% ART interruption, 6.6% short-term viremia, 5.8% confirmed VF without switch, and 2.4% confirmed VF with switch, or a total of 37.4% with VF for any reason (Fig. 1). Of 2,010 patients with VF, 24% had never achieved VL ≤200 copies/mL. Overall VF rates were higher for women vs. men (SHR 1.30) and Black vs. White patients (SHR 1.45), and patients with lower CD4 counts at ART initiation (SHR 0.90 per 100-cell increase) [all P<0.05]. Associations varied by VF reason. Black vs. White patients had higher rates of confirmed VF with switch

(SHR 1.99, 95% CI 1.33–2.98) but similar ART interruption rates. Patients on an NNRTI- vs. INSTI-based regimen had lower rates of unconfirmed VF (SHR 0.89, 95% CI 0.74–1.06), but higher rates of confirmed VF with switch (SHR 2.48, 95% CI 1.51–4.09).

**Conclusion:** One-fifth of ART initiators experienced viremia within 2 years. VF leading to an ART change was rare and more likely for patients initiating NNRTI-based regimens. Efforts to prevent viremia post-ART initiation should promote continuous ART and care engagement.

Figure 1. Stacked cumulative incidence curves of virologic failure (VF) by category among 6810 ART initiators in the US, 2008-2018.



**411 SECOND ANTIRETROVIRAL THERAPY REGIMEN IN VIREMIC PEOPLE WITH HIV IN THE US, 2008-2018**

Thibaut Davy-Mendez<sup>1</sup>, Sonia Napravnik<sup>2</sup>, David A. Wohl<sup>2</sup>, Ellen F. Eaton<sup>3</sup>, Richard Moore<sup>4</sup>, Edward R. Cachay<sup>5</sup>, Katerina Christopoulos<sup>1</sup>, George A. Yendewa<sup>6</sup>, Kenneth H. Mayer<sup>7</sup>, Mari M. Kitahata<sup>8</sup>, Joseph J. Eron<sup>2</sup>, for the Centers for AIDS Research Network of Integrated Clinical Systems

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>4</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>5</sup>University of California San Diego, San Diego, CA, USA, <sup>6</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>7</sup>The Fenway Institute, Boston, MA, USA, <sup>8</sup>University of Washington, Seattle, WA, USA

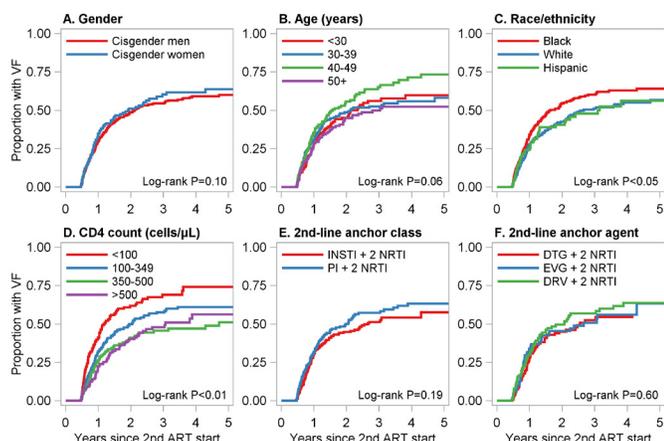
**Background:** Improvements in antiretroviral therapy (ART) have reduced first-line virologic failure rates, but little is known about prescription patterns and outcomes of subsequent ART in the US.

**Methods:** Among patients who first initiated ART in 7 HIV clinical cohorts 2008–2018, we examined patients who initiated second ART, defined as a new anchor antiretroviral (ARV) agent >8 months after initial ART start while viremic (latest viral load [VL] >200 copies/mL in past 90 days). We estimated time from second ART initiation to virologic failure (VF), defined as the first VL >200 copies/mL after 24 weeks, stratified by demographic and clinical characteristics, using Kaplan-Meier methods and log-rank tests.

**Results:** Of 705 eligible patients (75% cisgender men, 23% cisgender women, 54% Black, 31% White, 12% Hispanic), most first initiated ART prior to 2011 (54%) and with an NNRTI- (47%) or PI-based (29%) regimen. The median time between first and second ART was 2.7 years (IQR 1.5–4.5). Prior to second ART initiation, 39% of patients were continuously on their first regimen, 44% experienced an ART interruption, and 17% an ART change; overall 23% had never achieved VL ≤200 copies/mL. At second ART initiation, the median age was 39 years (30–49), CD4 count 304 cells/μL (131–470), and VL 21,900 copies/mL (3,300–71,000). The most frequent second regimens were 2 NRTIs in combination with an INSTI (38%), a PI (24%), an NNRTI (8%), both an INSTI and PI (6%), or both an NNRTI and PI (3%). The most frequently prescribed

ARVs were DTG (47%) and EVG (31%) for 398 InSTI-containing regimens, DRV (77%) for 308 PI-containing regimens, and RPV (48%) and EFV (30%) for 135 NNRTI-containing regimens. Two years after second ART initiation, 48.9% (95% CI 45.1–53.0) of patients had experienced virologic failure. Time to VF on second ART did not differ significantly by gender or age (Fig. 1A–B, both  $P > 0.05$ ) but was shorter for Black patients and patients with lower CD4 cell counts (Fig. 1C–D, both  $P < 0.05$ ). There were no significant differences in time to VF between the most frequent second regimens, by anchor class or agent (Fig. 1E–F, both  $P > 0.05$ ).

**Conclusion:** In 7 cohorts across the US, viremic patients initiating second ART in 2008–2018 were most frequently prescribed a 3-drug regimen containing an InSTI or a PI. Virologic failure on second ART was common and higher among patients who were Black or had lower CD4 counts. Preliminary analyses did not show differences between the most commonly used second ART regimens.



activation (CD8+CD38+ T cells, CD8+CD38+DR+) and apoptotic (annexin-V) markers were similar at baseline and declined significantly and similarly in both ART arms ( $P > 0.05$  for all comparisons). A greater reduction in shCD14 marker in patients treated with DTG was found (-802 [-1302; -398] vs. -396 [-924, 0.00] ng/mL;  $p = 0.011$ ).

**Conclusion:** DTG-based ART was as effective as and had fewer discontinuations than DRV/r-based ART in very advanced ART-naïve HIV-1-infected patients and superior to the bPI regimen in reducing the bacterial translocation

| mITT analysis   | Dolutegravir<br>N=52 | Darunavir/r<br>N=49 | p-value |
|---|----------------------|---------------------|---------|
| Age, yr., median (IQR)                                  | 40 (30;48)           | 41 (34;46)          | NA*     |
| Male gender, n (%)                                      | 44 (87)              | 46 (88.5)           |         |
| Men who have sex with men (MSM), n (%)                  | 31 (60)              | 25 (51)             |         |
| Baseline AIDS-defining events (ADE), n (%)              | 22 (42)              | 24 (46)             |         |
| Baseline RNA HIV VL, median (IQR) log <sub>10</sub> /mL | 5.47 (4.79;6.10)     | 5.67 (5.14;6.12)    |         |
| Baseline CD4, median (IQR) cells/mm <sup>3</sup>        | 41 (18; 67)          | 30 (11; 54)         |         |
| 48-wk CD4 increase (median delta, IQR)                  | 172.50 (118; 255)    | 157 (66; 277)       | 0.430   |
| 48-wk RNA HIV VL <50 copies/mL, n (%)                   | 40 (77)              | 31 (63)             | 0.191   |
| IRIS, n (%)   | 5 (10)               | 6 (12)              | 0.911   |
| New ADEs/death, n (%)                                   | 4 (8)                | 6 (12)              | 0.666   |
| Treatment discontinuation (any reason), n (%)           | 4 (8)                | 12 (24.5%)          | 0.029   |

\*NA: not applicable for baseline measurements

**413 D/C/F/TAF VS DTG/ABC/3TC FOR INITIAL TREATMENT IN HIV+ ADULTS: A RANDOMIZED STUDY**

**Daniel Podzamczar<sup>1</sup>**, Rafael Mican<sup>2</sup>, Juan M. Tiraboschi<sup>1</sup>, Joaquín Portilla<sup>3</sup>, Pere Domingo<sup>4</sup>, Josep Maria Llibre<sup>5</sup>, Esteve Ribera<sup>6</sup>, María Jesús Vivancos<sup>7</sup>, Luis Morano<sup>8</sup>, Mar Masía<sup>9</sup>, Cristina Gómez-Ayerbe<sup>10</sup>, Antonio Navarro<sup>1</sup>, Ana Caicedo<sup>11</sup>, Santiago Moreno<sup>7</sup>, for the SYMTRI Study Group (PreEC/RIS-57)

<sup>1</sup>Hospital Universitario de Bellvitge, Barcelona, Spain, <sup>2</sup>Hospital Universitario La Paz, Madrid, Spain, <sup>3</sup>Hospital General Universitario de Alicante, Alicante, Spain, <sup>4</sup>Hospital de Sant Pau, Barcelona, Spain, <sup>5</sup>Hospital Germans Trias i Pujol, Barcelona, Spain, <sup>6</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, <sup>7</sup>Hospital Ramón y Cajal, Madrid, Spain, <sup>8</sup>Hospital Universitario Alvaro Cunqueiro, Vigo, Spain, <sup>9</sup>Hospital General Universitario de Elche, Elche, Spain, <sup>10</sup>Hospital Universitario Virgen de la Victoria, Málaga, Spain, <sup>11</sup>Red de Investigación en SIDA, Barcelona, Spain

**Background:** Integrase inhibitors (InSTI) are considered the preferred core for initial ART in HIV-1 infected pts. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) is an alternative regimen with high efficacy rates that has never been compared with InSTI-based regimens in randomized trials. We performed a head to head comparison between D/C/F/TAF and dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in ARV-naïve pts, both administered as single tablet regimens (STR)

**Methods:** Adult (> 18y) HIV-infected naïve pts (HLA B5701 and HBV negative), with viral load (VL)  $\geq 500$  c/mL, from 27 Spanish hospitals, were randomized after stratifying by viral load (< or  $\geq 100,000$  c/mL) and CD4 cells (< or  $\geq 200$  cells/uL) between September 2018 and 2019. Clinical and analytical assessments were performed at weeks 0, 4, 12, 24 and 48. Primary endpoint was VL < 50 c/mL at week 48 (ITT exposed analysis, with a non-inferiority margin of 10%). Calculated sample size (10% lost to FU) was 316 pts. (EudraCT 2018-001645-14)

**Results:** Ten pts did not come back after enrollment visit (7 in D/C/F/TAF vs 3 in DTG/ABC/3TC arms). Groups were well balanced in the baseline characteristics and 306 patients were included in the ITTe analysis (151 and 155). 94% were male, median age 35 years, 79% were MSM, median VL 64,848 c/mL (40% > 100,000 c/mL), CD4 408/uL (13% < 200/uL, 27% 200-350), HCV 3%, weight 73 kg, BMI 24 kg/m<sup>2</sup>. At 48 weeks, 79% (D/C/F/TAF) vs 82% (DTG/3TC/ABC) had VL < 50 c/mL (difference -2.4%, 95%CI -11.3 to 6.6). Virologic failure was 8% vs 4%; drug discontinuation due to adverse events was 4% (n=6, 5 skin rashes, 1 pulmonary TB) vs 6% (n=9, 3 neuropsychiatric symptoms, 2 muscle complaints, 2 gastrointestinal, 1 skin rash, 1 neoplasm); lost to follow-up 8% in each arm. In the per protocol analysis (pts reaching 48 weeks with the allocated drug regimen), 94% vs 96% patients had VL < 50 c/mL (difference -2%, 95%CI -8.1 to 3.5). Three sensitivity ITT analyses were performed (Table 1). No differences were found in CD4 count increase (+226 vs +260/uL,  $p = 0.10$ ), weight increase (3.0 vs 2.9 kg,  $p = 0.8$ ), or BMI, at week 48 (1.0 vs 0.96 kg/m<sup>2</sup>,  $p = 0.8$ )

**Conclusion:** D/C/F/TAF administered as a STR did not reach statistical non-inferiority vs. DTG/ABC/3TC in the ITTe analysis, nor in ITT sensitivity analyses. Both regimens were well tolerated with a similar increase in CD4 counts, weight or BMI. D/C/F/TAF is an efficacious and well tolerated alternative to InSTI regimens in ARV-naïve pts

**412 DOLUTEGRAVIR VS DARUNAVIR/R-BASED ART IN VERY ADVANCED PATIENTS: 48-WEEK RESULTS**

**Jose M. Miro<sup>1</sup>**, Ferran Torres<sup>1</sup>, Christian Manzano<sup>1</sup>, Eva Bonfill<sup>1</sup>, Vicenç Falcó<sup>2</sup>, Pere Domingo<sup>3</sup>, Daniel Podzamczar<sup>4</sup>, Roger Paredes<sup>5</sup>, Lluís Forcé<sup>6</sup>, Adrià Curran<sup>2</sup>, Mar Gutierrez<sup>2</sup>, María Saumoy<sup>4</sup>, Nuria Climent<sup>1</sup>, Francisco Lozano<sup>1</sup>, Montserrat Plana<sup>1</sup>

<sup>1</sup>Hospital Clinic of Barcelona, Barcelona, Spain, <sup>2</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, <sup>3</sup>Hospital de Sant Pau, Barcelona, Spain, <sup>4</sup>Hospital Universitario de Bellvitge, Barcelona, Spain, <sup>5</sup>Hospital Germans Trias i Pujol, Barcelona, Spain, <sup>6</sup>Hospital de Mataró, Mataró, Spain

**Background:** Information on the impact of dolutegravir (DTG)-based antiretroviral therapy (ART) in very advanced patients is limited in terms of clinical, immune reconstitution and virological outcomes, bacterial translocation, inflammation and immune activation. Also, whether the impact on bacterial translocation varies with the ART-regimen type is unknown, as boosted protease inhibitors (bPI) and integrase inhibitors (InSTI) have different metabolic patterns in the gut.

**Methods:** The Advanz-4 trial (NCT02337322) is a multicenter RCT with 104 HIV-1-infected antiretroviral-naïve patients with <100 CD4+ cells/mm<sup>3</sup> randomly assigned 1:1 to DTG (N=52) or darunavir-ritonavir (DRV/r) (N=52) plus abacavir and lamivudine at standard doses. The primary endpoint was median increase in CD4 cell count at week 48. Secondary endpoints were the proportion of patients with plasma HIV-1 RNA viral load (VL) <50 copies/mm<sup>3</sup>, bacterial translocation, inflammation, immune activation, adverse events, IRIS, HIV disease progression and death. 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 (SAS Inst. Inc., Cary, NC, USA).

**Results:** Baseline epidemiological, clinical, immunological and virological features and main results are depicted in the table. Median (IQR) increase in the CD4 count after 48 weeks was +172 (118; 255) and 157 (66; 277) cells/mm<sup>3</sup> in the DTG and DRV/r arms, respectively ( $p = 0.430$ ). Plasma HIV-1 RNA VL suppression (<50 copies/mL) was significantly faster in the DTG arm at 4 and 12 weeks. At 48 weeks, the rate of suppressed patients was similar (77% vs. 63%,  $p = 0.191$ ). IRIS and new AIDS defining events were low and similar in both arms. Only one patient died in the DRV/r arm. Treatment discontinuation was higher in the DRV/r arm (24.5% vs. 8%,  $p = 0.029$ ). There were four virological failures (1 in DTG and 3 in DRV/r arm). Inflammation (TNF-alpha, IL-6, hsCRP), immune

Table 1. Efficacy rates (VL <50 c/mL) in the ITTe snapshot and other analyses

| Analyses (n pts)            | D/C/F/TAF | DTG/ABC/3TC | p value | Treatment diff. (95%CI)* |
|-----------------------------|-----------|-------------|---------|--------------------------|
| ITTe (306)                  | 79%       | 82%         | 0.70    | -2.4% (-11.3 to 6.6)     |
| Per protocol (258)          | 94%       | 96%         | 0.60    | -2% (-8.1 to 3.5)        |
| <b>Sensitivity analyses</b> |           |             |         |                          |
| ITT (316)                   | 76%       | 80%         | 0.42    | -4.3% (-13.4 to 4.8)     |
| ITTe CV<200 (306)           | 81%       | 84%         | 0.72    | -2.2% (-10.8 to 6.4)     |
| ITT M=E**(265)              | 91%       | 95%         | 0.27    | -4.1% (-10.9 to 2.2)     |

\*Differences in percentages of patients with HIV-1 RNA of less than 50 copies/mL or less than 200 c/mL, between treatment groups and their 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HIV-1 RNA stratum (<100000 vs ≥100000 copies/mL) and baseline CD4 stratum (<200 vs ≥200/uL).

\*\*M=E, missing=excluded

#### 414 DURABLE EFFICACY OF DTG+3TC IN GEMINI-1&2: YEAR 3 SUBGROUP ANALYSES

**Chloe Orkin**<sup>1</sup>, Norma Porteiro<sup>2</sup>, Mezgebe Berhe<sup>3</sup>, Robin H. Dretler<sup>4</sup>, Federico Pulido<sup>5</sup>, Shu-Hsing Cheng<sup>6</sup>, Cristiana Oprea<sup>7</sup>, Margarate A. Johnson<sup>8</sup>, Svetlana Kizhlo<sup>9</sup>, Jörg Sievers<sup>10</sup>, Choy Man<sup>11</sup>, Rimgaile Urbaityte<sup>12</sup>, Mark Underwood<sup>11</sup>, Brian Wynne<sup>11</sup>, Jean A. Van Wyk<sup>10</sup>

<sup>1</sup>Queen Mary University of London, London, UK, <sup>2</sup>Fundacion IDEAA, Buenos Aires, Argentina, <sup>3</sup>Texas Infectious Diseases Consultants, Dallas, TX, USA, <sup>4</sup>Infectious Disease Specialists of Atlanta, Decatur, GA, USA, <sup>5</sup>Hospital Universitario 12 de Octubre, Madrid, Spain, <sup>6</sup>Taoyuan General Hospital, Taoyuan, Taiwan, <sup>7</sup>Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania, <sup>8</sup>Royal Free Hospital, London, UK, <sup>9</sup>Centre for Prevention and Control of AIDS and Infectious Diseases, St. Petersburg, Russian Federation, <sup>10</sup>ViiV Healthcare, Brentford, UK, <sup>11</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>12</sup>GlaxoSmithKline, Uxbridge, UK

**Background:** In the GEMINI-1 & GEMINI-2 studies (ClinicalTrials.gov: NCT02831673 & NCT02831764), dolutegravir + lamivudine (DTG+3TC) was non-inferior to the 3-drug regimen of DTG + tenofovir/emtricitabine (TDF/FTC) in achieving plasma HIV-1 RNA <50 c/mL in treatment-naïve adults at Weeks 48, 96 and 144.

**Methods:** GEMINI-1&2 are identical, global, double-blind, multicenter Phase III studies. Participants with screening HIV-1 RNA ≤500,000 c/mL and no major viral resistance mutations to NRTIs, NNRTIs or PIs were randomised to once-daily DTG+3TC or DTG+TDF/FTC, stratified by plasma HIV-1 RNA and CD4+ cell count. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm). We present a secondary endpoint analysis of efficacy at Week 144 by baseline disease and demographic characteristics. For the overall population, estimates and confidence intervals were based on a stratified analysis using Cochran-Mantel-Haenszel weights.

**Results:** 714 and 719 adults were randomised and treated in GEMINI-1&2, respectively. Using a 10% non-inferiority margin, DTG+3TC was non-inferior to DTG+TDF/FTC at Week 144 in both GEMINI-1&2 and in the pooled analysis. Response rates across baseline HIV-1 RNA subgroups were high and similar in both arms in the pooled analysis, including in participants with baseline HIV-1 RNA >100,000 c/mL (Table 1). Results were also generally consistent regardless of age, sex or race. While response rates remained lower in DTG+3TC compared to DTG+TDF/FTC participants with CD4+ ≤200 cells/mm<sup>3</sup>, differences were smaller than at Weeks 48 and 96; most reasons for non-response were unrelated to virologic efficacy or treatment regimen. Across both studies, 12 participants on DTG+3TC and 9 on DTG+TDF/FTC met confirmed virologic withdrawal (CVW) criteria through Week 144; none had treatment-emergent INSTI or NRTI resistance mutations. One non-CVW DTG+3TC participant with reported non-adherence developed M184V at Week 132 and added R263R/K at Week 144, conferring a 1.8-fold change in DTG susceptibility.

**Conclusion:** In GEMINI-1&2, DTG+3TC was non-inferior to DTG+TDF/FTC in treatment-naïve adults at Week 144, demonstrating durable efficacy. The subgroup efficacy results at Week 144 were generally consistent with overall study results and further demonstrate that DTG+3TC is an effective initial treatment for HIV-infected patients across a spectrum of disease characteristics and patient populations.

Table 1. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 144: Snapshot Analysis by Subgroups – ITT-E Population

|  | POOLED GEMINI-1&2 |                     |
|--|-------------------|---------------------|
|  | DTG+3TC n/N (%)   | DTG+TDF/FTC n/N (%) |
| Overall population                     | 584/716 (82)      | 599/717 (84)        |
| Adjusted difference (95% CI)           | -1.8 (-5.8, 2.1)  |                     |
| Age (years)                            | <35               | 337/420 (80)        |
|  | 35 to <50         | 193/231 (84)        |
|  | ≥50               | 54/65 (83)          |
| Sex                                    | Female            | 84/113 (74)         |
|  | Male              | 500/603 (83)        |
| Race                                   | White             | 409/484 (85)        |
|  | African heritage  | 60/90 (67)          |
|  | Asian             | 56/71 (79)          |
|  | Other             | 59/71 (83)          |
| Baseline HIV-1 RNA (c/mL)              | ≤100,000          | 469/576 (81)        |
|  | >100,000          | 115/140 (82)        |
| Baseline CD4+ (cells/mm <sup>3</sup> ) | ≤200              | 42/63 (67)          |
|  | >200              | 542/653 (83)        |

#### 415 4-YEAR OUTCOMES OF B/F/TAF IN TREATMENT-NAÏVE ADULTS

**Kimberly Workowski**<sup>1</sup>, Chloe Orkin<sup>2</sup>, Paul Sax<sup>3</sup>, Debbie Hagins<sup>4</sup>, Ellen Koenig<sup>5</sup>, Jeffrey Stephens<sup>6</sup>, David A. Wohl<sup>7</sup>, Adriano Lazzarin<sup>8</sup>, Samir Gupta<sup>9</sup>, Hailin Huang<sup>10</sup>, Rima K. Acosta<sup>10</sup>, Jason Hindman<sup>10</sup>, Diana Brainard<sup>10</sup>, Sean E. Collins<sup>10</sup>, Hal Martin<sup>10</sup>  
<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Barts Health NHS Trust, London, UK, <sup>3</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>4</sup>Chatham County Health Department, Savannah, GA, USA, <sup>5</sup>Instituto Dominicano de Estudios Viroológicos, Santo Domingo, Dominican Republic, <sup>6</sup>Mercer University, Macon, GA, USA, <sup>7</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>8</sup>San Raffaele Hospital Milan, Milan, Italy, <sup>9</sup>Indiana University, Indianapolis, IN, USA, <sup>10</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a guideline-recommended single-tablet regimen for people with HIV-1 (PWH). We present cumulative outcomes from open-label extension (OLE) that followed 144 Weeks (W) of blinded treatment in phase 3 studies in treatment-naïve PWH.

**Methods:** We conducted 2 randomized, double-blind, phase 3 studies of B/F/TAF in treatment-naïve adults – Study 1489: B/F/TAF vs dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) and Study 1490: B/F/TAF vs DTG+F/TAF. After completing 144W of blinded treatment, participants were offered to continue on B/F/TAF for 96W in the OLE. Efficacy was assessed as the proportion with HIV-1 RNA <50 copies/mL at each visit after starting B/F/TAF using missing=excluded (M=E) analysis; safety by adverse events (AEs) and laboratory results. Bone mineral density (BMD) in OLE was measured in those randomized to B/F/TAF in Study 1489. We present cumulative results for all participants treated with B/F/TAF in the randomized or OLE phases through a maximum of 192 weeks of follow up (i.e. OLE W48). The final phase of this study will complete once all participants reach a total of 240 weeks (i.e. OLE W96).

**Results:** In Study 1489, 314 participants were randomized to B/F/TAF and 315 to DTG/ABC/3TC; 252 and 254 entered the OLE. In Study 1490, 320 were randomized to B/F/TAF and 325 to DTG+F/TAF; 254 and 265 entered the OLE. Efficacy was >98% after W48 at each study visit through W192 in both studies. Across both studies, only one participant experienced an AE that led to drug discontinuation during the OLE analysis window. Grade 3 or 4 drug-related AEs were rare (Table). There were no discontinuations due to renal AEs. In participants initially randomized to B/F/TAF, the median change in weight from baseline to W192 was 4.6 kg in Study 1490 and 5.0 kg in Study 1489. The mean percent changes (SD) in hip and spine BMD through W192 were -1.5% (4.9) and -0.9% (5.2), respectively. 13% of participants with baseline osteopenia in hip and 3% with osteopenia of the spine improved to normal at W192, 4% with normal baseline hip and 6% with normal baseline spine BMD progressed to osteopenia and none developed osteoporosis.

**Conclusion:** Over 4 years of follow-up in treatment-naïve participants, B/F/TAF was safe and highly efficacious. Similar outcomes were demonstrated in participants who switched from DTG-containing regimens to B/F/TAF. These results confirm long term safety and efficacy of B/F/TAF.

|  | Study 1489        |                                | Study 1490        |                              |
|--|-------------------|--------------------------------|-------------------|------------------------------|
|  | B/F/TAF (n=314)   | DTG/ABC/3TC to B/F/TAF (n=254) | B/F/TAF (n=520)   | DTG+F/TAF to B/F/TAF (n=265) |
| <b>Baseline Characteristics at B/F/TAF Start</b>   |                   |                                |                   |                              |
| Median age (Q1, Q3)                                | 31 (25, 41)       | 36 (30, 45)                    | 36 (19, 80)       | 39 (30, 49)                  |
| Female sex   | 9%                | 11%                            | 13%               | 10%                          |
| African descent                                    | 31%               | 37%                            | 30%               | 30%                          |
| Latinx/Hispanic                                    | 23%               | 21%                            | 26%               | 28%                          |
| <b>Efficacy and Safety from B/F/TAF Start</b>      |                   |                                |                   |                              |
| HIV-1 RNA <50 c/mL [n/N]†                          | 99% (235/237)     | 100% (212/212)                 | 99% (241/243)     | 99% (224/225)                |
| Median duration of exposure to B/F/TAF, W (Q1, Q3) | 215 (210, 223)    | 57 (55, 58)                    | 213 (210, 218)    | 56 (55, 58)                  |
| Grade 3 or 4 drug related AEs                      | 1%                | 0%                             | 1.6%              | <1%                          |
| eGFR, median change, mL/min (Q1, Q3)               | -7.6 (-21.2, 2.3) | +1.0 (-7.4, 9.5)               | -8.4 (-16.8, 3.0) | -0.4 (-7.3, 9.4)             |
| Total cholesterol: HDL ratio                       | -0.1 (-0.6, 0.4)  | +0.1 (-0.2, 0.6)               | 0 (-0.6, 0.5)     | +0.1 (-0.2, 0.5)             |

†Missing=excluded analysis at W192 for the groups randomized to B/F/TAF and W48 of treatment with B/F/TAF in the OLE for switch groups.

**416 WEEK 96 ANALYSIS OF VIRAL BLIPS FROM A PHASE 2B TRIAL OF ISLATRAVIR AND DORAVIRINE**

**Chloe Orkin**<sup>1</sup>, Jean-Michel Molina<sup>2</sup>, Yazdan Yazdanpanah<sup>3</sup>, Carolina Chahin Anania<sup>4</sup>, Joseph J. Eron<sup>5</sup>, Stephanie O. Klopfer<sup>6</sup>, Karen A. Eves<sup>6</sup>, Deborah A. Hepler<sup>6</sup>, Carey Hwang<sup>6</sup>, Todd A. Correll<sup>6</sup>

<sup>1</sup>Queen Mary University of London, London, UK, <sup>2</sup>University of Paris Diderot, Paris, France, <sup>3</sup>Hopital Bichat Claude Bernard, Paris, France, <sup>4</sup>Hospital Hernan Henriquez Aravena de Temuco, Temuco, Chile, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>Merck & Co, Inc, Kenilworth, NJ, USA

**Background:** Islatravir (ISL, MK-8591) is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection. Previously we showed that ISL+DOR demonstrated efficacy in maintaining viral suppression and was well tolerated through week 96 in a Phase 2b trial. Rates of protocol defined virologic failure (PDVF) were low across all groups. Here we report on an analysis of blip frequency—a sensitivity marker for efficacy.

**Methods:** In a Phase 2b trial in treatment-naïve adults with HIV-1, participants were randomized to receive ISL (0.25, 0.75 or 2.25 mg) + DOR (100 mg) and lamivudine (3TC, 300 mg) QD, or a fixed-dose combination of DOR, 3TC and tenofovir disoproxil fumarate (DOR/3TC/TDF). Participants receiving ISL achieving HIV-1 RNA <50 copies/mL at week 20 or later stopped 3TC at the next study visit to transition to the two-drug regimen for Part 2 of the trial. For this current analysis we analyzed viral blip frequency for participants who entered Part 2 of the trial through week 96. A viral blip was defined as an HIV-1 RNA ≥50 copies/mL value observed between two values of <50 copies/mL after achieving initial response.

**Results:** 114 participants entered Part 2 of the trial and were included in the analysis. During Part 2 of the trial through week 96, a higher percentage of participants on the three-drug regimen in the DOR/3TC/TDF group experienced viral blips as compared to participants on the two-drug regimen in the combined ISL groups; 4 blip episodes occurred in 4 out of 28 participants (14.3%) in the DOR/3TC/TDF group as compared to 8 blip episodes in 7 of 86 participants (8.1%) in the combined ISL groups (Table 1). Of the participants with viral blips, 5 of 7 participants in the combined ISL groups and 0 out of 4 participants in the DOR/3TC/TDF group had baseline HIV-1 RNA >100,000 c/mL. All participants with viral blips, including those with high baseline HIV-1 RNA levels, re-suppressed by the next study visit and remained suppressed through week 96. None of the participants with viral blips had subsequent viral rebound or PDVF. **Conclusion:** Viral blips were relatively rare for all treatment groups and were not associated with a loss of virologic suppression or PDVF.

Table 1: Frequency of Viral blips for participants who entered Part 2 of the trial

| Time Period  | Parameter                                | ISL 0.25 mg + DOR + 3TC QD | ISL 0.75 mg + DOR + 3TC QD | ISL 2.25 mg + DOR + 3TC QD | Combined ISL 12.2 | DOR/3TC/TDF |
|--|--|----------------------------|----------------------------|----------------------------|-------------------|-------------|
|  |  | N=29                       | N=30                       | N=27                       | N=86              | N=28        |
| Part 2 through Week 96 (ISL groups 2-drug regimen) | Number of Participants with Blips, n (%) | 3 (10.3)                   | 1 (1.3)                    | 3 (11.1)                   | 7 (8.1)           | 4 (14.3)    |
|  | Number of Distinct Blip Episodes         | 4                          | 1                          | 3                          | 8                 | 4           |

**417 SWITCHING TO DTG/3TC FDC IS NONINFERIOR TO TBR FOR 96 WEEKS: TANGO SUBGROUP ANALYSES**

**Paul Benson**<sup>1</sup>, Clifford A. Kinder<sup>2</sup>, María Jesús Pérez-Eliás<sup>3</sup>, Don E. Smith<sup>4</sup>, Stefan H. Scholten<sup>5</sup>, Mounir Ait-Khaled<sup>6</sup>, Keith A. Pappa<sup>7</sup>, Ruolan Wang<sup>7</sup>, Jonathan Wright<sup>8</sup>, Brian Wynne<sup>7</sup>, Michael Aboud<sup>6</sup>, Jean A. Van Wyk<sup>6</sup>, Kimberly Smith<sup>7</sup>

<sup>1</sup>Be Well Medical Center, Berkley, MI, USA, <sup>2</sup>AIDS Healthcare Foundation - The Kinder Medical Group, Miami, FL, USA, <sup>3</sup>Hospital Universitario Ramón y Cajal, Madrid, Spain, <sup>4</sup>Albion Centre, Sydney, Australia, <sup>5</sup>Praxis Hohenstaufenring, Cologne, Germany, <sup>6</sup>ViiV Healthcare, Brentford, UK, <sup>7</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>8</sup>GlaxoSmithKline, Uxbridge, UK

**Background:** The 2-drug regimen (2DR) of DTG/3TC reduces the number of antiretroviral agents taken by individuals treated for HIV-1 infection, when compared to traditional 3DRs. DTG/3TC is non-inferior to DTG+TDF/FTC in HIV-1 infected ART-naïve adults (GEMINI) through Week 144 and in ART-experienced, virologically suppressed participants switching from a TAF-based 3/4DR

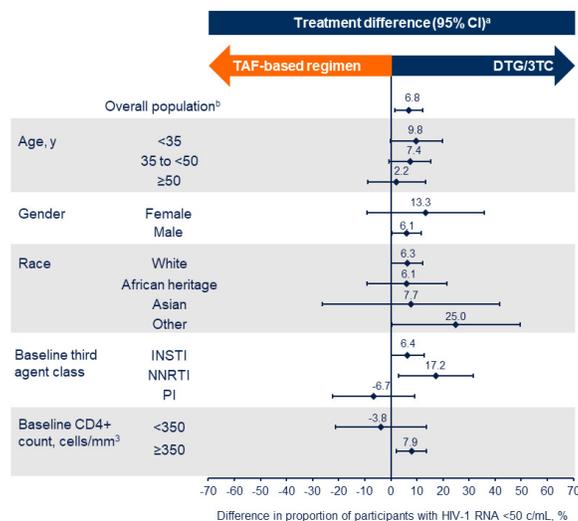
(TANGO) through Week 96. Here we present a key Week 96 secondary endpoint from the TANGO study: Snapshot virologic success by baseline regimen third agent class, disease and demographic characteristics.

**Methods:** TANGO is a randomized, open-label, multicenter, non-inferiority Phase III study evaluating the efficacy and safety of switching to DTG/3TC once daily versus remaining on a current TAF-based regimen in HIV-1 infected adults, with HIV-1 RNA <50 c/mL for >6 months, on a TAF-based regimen for at least 3 months and without prior virologic failure or historical NRTI or INSTI major resistance mutations, were eligible to participate. Randomization was stratified by baseline 3rd agent class: PI, NNRTI, INSTI. The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (FDA Snapshot algorithm, Intention To Treat-Exposed [ITT-E] population) with secondary analyses at Week 96.

**Results:** 741 randomized/exposed participants (DTG/3TC: 369; TBR: 372) were included. Snapshot success rates across subgroups were generally consistent with the overall TANGO Week 96 study results and were similar between arms (Figure). Zero participants on DTG/3TC and 3 participants (<1%) on TBR met confirmed virologic withdrawal criteria with no resistance mutations observed at failure.

**Conclusion:** Switching to DTG/3TC FDC was non-inferior to continuing a TAF-based 3DR in maintaining virologic suppression in HIV-1 infected ART-experienced adults through Week 96. Efficacy by subgroups was consistent with overall Week 96 study results, demonstrating that switching from TAF-based regimens to DTG/3TC is effective at maintaining virologic suppression regardless of baseline regimen, patient or disease characteristics.

Figure. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 96: Snapshot Analysis by Subgroups – ITT-E Population



<sup>a</sup>Unadjusted difference for subgroups calculated by proportion on DTG/3TC – proportion on TAF-based regimen. <sup>b</sup>Adjusted difference for overall population (DTG/3TC – TAF-based regimen) and 95% confidence intervals are based on a stratified analysis (adjusting for baseline third agent class) using Cochran-Mantel-Haenszel weights (meeting non-inferiority based on 8% margin).

**418 MISSING DATA, MISSING DIVERSITY: PARTICIPANT DEMOGRAPHICS IN INDUSTRY STUDIES 2010-20**

**Liz Barr**<sup>1</sup>, Michael J. Dorosh<sup>1</sup>, Murray Penner<sup>2</sup>, Moises Agosto<sup>1</sup>, Danielle Campbell<sup>1</sup>, Bob Huff<sup>1</sup>, Rick Guasco<sup>1</sup>, Andy Kaytes<sup>1</sup>, David Palm<sup>3</sup>, for the AIDS Treatment Activists Coalition

<sup>1</sup>AIDS Treatment Activists Coalition, Denver, CO, USA, <sup>2</sup>AIDS Treatment Activists Coalition, Washington, DC, USA, <sup>3</sup>AIDS Treatment Activists Coalition, Research Triangle Park, USA

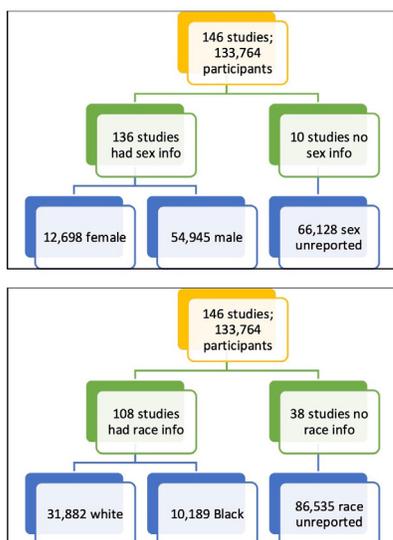
**Background:** Public attention on the need for participant diversity is high, particularly in light of the recent wave of journal and governmental policies requiring studies to report varying elements of participant diversity (sex, race, age) and the FDA's recent decisions to limit certain PrEP indications by sex. AIDS Treatment Activists Coalition (ATAC) is a US-based coalition of AIDS activists who meets regularly with pharmaceutical companies to bring an expert community perspective into the development of new HIV drugs and the utilization of HIV therapies. ATAC undertook a systematic analysis of participant diversity in Industry-sponsored studies for four active companies in HIV research and development (R&D): Gilead Sciences (Gilead), Janssen, Merck, and ViiV

Healthcare (ViiV). The primary objective of this analysis was to characterize participant demographics in efficacy and registrational pharmaceutical studies (Phase II, III, IV, and Observational studies) from 2010–2020 that were sponsored by these four companies.

**Methods:** A systematic search of clinicaltrials.gov for any studies related to HIV drugs under development by the four companies during the study time period (2010-2020) was completed. Search results were screened for relevance. Registry listings for studies in final dataset (N=146) were reviewed, and study information (including phase, # of participants, dates, location, and demographics when available) were recorded. Analyses were performed in Excel to characterize trends in participant diversity by company, study phase, study location, and time period.

**Results:** Participant sex, which was generally reported to clinicaltrials.gov, suggests that male participants are over-recruited by 34%. Race-specific data was unreported for 65% of studies, and, when reported, suboptimal. Geographic diversity was lacking, as a majority (75%) of study sites were in the United States.

**Conclusion:** ATAC recommends that industry: Enroll more cisgender and transgender women, ensuring women participants are representative of the global and local HIV epidemics in race, ethnicity, and age; Enroll participants that reflect the racial and ethnic diversity of PLWHIV – including Black, Hispanic/Latinx, and Native American participants in the United States; Disaggregate data by sex, gender, race, ethnicity, and age. Disaggregate transgender women from MSM in reporting; Replace upper age limits with specific health related exclusion criteria; Prioritize enrollment of participants from impacted communities



#### 419 W96 EFFICACY OF 4/7 DAYS MAINTENANCE ART STRATEGY: ANRS-170 QUATUOR TRIAL

**Roland Landman**<sup>1</sup>, Lambert Assoumou<sup>2</sup>, Sidonie Lambert-Niclot<sup>3</sup>, Jonathan Bellet<sup>4</sup>, Karine Amat<sup>5</sup>, Clotilde Allavena<sup>6</sup>, Christine Katlama<sup>7</sup>, Karine Lacombe<sup>8</sup>, Jean-Michel Molina<sup>9</sup>, Yazdan Yazdanpanah<sup>10</sup>, Severine Gibowski<sup>11</sup>, Jean-Claude Alvarez<sup>12</sup>, Jacqueline Capeau<sup>13</sup>, Laurence Morand-Joubert<sup>3</sup>, Pierre De Truchis<sup>14</sup>  
<sup>1</sup>Institut de Médecine et Epidémiologie Appliquée Fondation Léon M Ba, Hôpital Bichat, PARIS, France, <sup>2</sup>Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, PARIS, France, <sup>3</sup>Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique Département de Virologie, Hôpital Saint-Antoine, PARIS, France, <sup>4</sup>AP-HP, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, Sorbonne Université, INSERM, PARIS, France, <sup>5</sup>Institut de Médecine et Epidémiologie Appliquée, Hôpital Bichat, PARIS, France, <sup>6</sup>Hôpital Hôtel-Dieu, Service des Maladies Infectieuses, NANTES, France, <sup>7</sup>Hôpital Pitié-Salpêtrière APHP, Service des Maladies Infectieuses, PARIS, France, <sup>8</sup>Hôpital Saint-Antoine APHP, Service des Maladies Infectieuses, PARIS, France, <sup>9</sup>Hôpital Saint-Louis APHP, Service des Maladies Infectieuses, PARIS, France, <sup>10</sup>Université de Paris, INSERM, IAME, Hôpital Bichat-Claude Bernard, Service de Maladies Infectieuses et Tropicales, AP-HP, PARIS, France, <sup>11</sup>ANRS-Inserm, PARIS, France, <sup>12</sup>Département de Pharmacologie, Hôpital R Poincaré APHP, Inserm U-1173, Université Paris-Ile de France Ouest, Garches 92, France, GARCHES, France, <sup>13</sup>Sorbonne Université, INSERM UMR\_S838 CRSA, Hôpital Tenon Service de Biochimie et Hormonologie, APHP, PARIS, France, <sup>14</sup>Hôpitaux Universitaires Paris-Ile de France-Ouest, Hôpital Raymond Poincaré APHP, Université Versailles-Saint-Quentin, GARCHES, France

**Background:** Intermittent treatment could improve the convenience, tolerability and cost of ART. We have previously demonstrated in the QUATUOR trial the non-inferiority of maintenance 4 days-a-week (4/7days) versus 7/7days in patients (pts) under triple therapy with either PI, NNRTI, or InSTI based regimen: 95.6% vs 97.2% treatment success at W48. ClinicalTrials.gov:NCT03256422. We report here the W96 results

**Methods:** Randomized, open-label, multicenter parallel trial evaluating the efficacy and safety of a maintenance 4/7days. Pts with plasma viral load (VL)<50 copies/mL for at least 12 months were randomly assigned in a 1:1 ratio to immediate switch to a 4/7days (4/7-I) at D0 or to a deferred switch to 4/7 days (4/7-D) at W48. The primary endpoint for the present analysis was the Kaplan-Meier estimated proportion of participants under the 4/7-days strategy (4/7-I group 0-96 weeks and 4/7-D group 48-96 weeks) with treatment success (VL<50 copies/mL and no treatment strategy modification) at week 96

**Results:** Overall, 621 pts on 4/7-days strategy were analyzed (318 in 4/7-I group and 303 in 4/7-D group). The 3rd agent drug class was NNRTI for 286 (46%), InSTI for 300 (48%), and PI for 35 (6%). At W96, therapeutic success with the 4/7-days strategy was 92.6% [95% CI 90.2-95.2] and virological failure (VF, defined as 2 consecutive VL ≥50 copies/mL) was 4.2% [2.2-6.3]. Of the 318 pts in the 4/7-I group, 14 underwent therapeutic failure including 6 VF until W48 and 11 after W48 (7 VF). Among the 303 pts who switched to 4/7-days strategy at W48, 10 had therapeutic failure (6 VF) after W48. Regarding the 3rd agent class, VF was observed in 5.3% [1.8-8.6] with NNRTI, and 2.4% [0.6-4.1] with InSTI at W96. Overall, among the 19 VF, drug resistance mutations appeared in 7 pts, 2 to nucleoside analogs (NA) alone, 4 to NA and NNRTI, 1 to NA and InSTI (raltegravir). No significant adverse events, biological changes or changes in the level of pro-inflammatory markers were observed with the 4/7-days strategy until W96, except a gain of +4 ml/min (IQR -2;+6) in eGFR, p<0.001

**Conclusion:** The efficacy result of 4/7-days strategy was sustained at W96, with a low rate of viral failure, particularly with InSTI based regimen. This 4 consecutive days-on and 3 days-off reduced the cost ART maintenance regimens and represents a real, workable, alternative to the recommended maintenance therapy

#### 420 STRUCTURAL BASIS FOR VIRAL RESISTANCE TO LONG-ACTING HIV-1 CAPSID INHIBITOR GS-6207

**Stephanie M. Bester**<sup>1</sup>, Reed Haney<sup>1</sup>, Daniel Adu-Ampratwum<sup>2</sup>, James Fuchs<sup>2</sup>, Mamuka Kvaratskhelia<sup>1</sup>

<sup>1</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>2</sup>The Ohio State University, Columbus, Ohio, USA

**Background:** GS-6207 (Lenacapavir, Gilead Sciences) is an experimental long-acting and highly potent HIV-1 capsid (CA) inhibitor. Viral breakthrough assays in cell culture identified a number of HIV-1 CA substitutions including M66I, Q67H, N74D and Q67H/N74D that confer substantial resistance to the inhibitor.

Furthermore, the Q67H capsid substitution has emerged in HIV-1 infected patients receiving GS-6207.

**Methods:** We have determined high-resolution x-ray crystal structures of cross-linked HIV-1 CA hexamers containing the following drug-resistant substitutions: M66I, Q67H, N74D and Q67H/N74D. In addition, we have determined the structure of CAQ67H/N74D in the complex with GS-6207.

**Results:** Our x-ray crystal structures have uncovered the following three distinct mechanisms for drug-resistance: i) the structure of the CAM66I hexamer reveals that the isoleucine's  $\beta$ -branched side chain extends further from the main chain and creates steric hindrance with respect to GS-6207; ii) the structures of the CAQ67H and CAQ67H/N74D hexamers show markedly different positioning of the histidine side chain compared with the glutamine in wild type CA hexamer + GS-6207. Specifically, the side chain of His67 is positioned into the inhibitor binding pocket and would therefore sterically hinder the binding of GS-6207 unless repositioned. The structure of the CAQ67H/N74D hexamer + GS-6207 reveals that the side chain of His67 is in fact repositioned to a similar conformation as Gln67 in wild type CA hexamer to accommodate GS-6207 within the binding pocket; iii) while the structure of the CAN74D hexamer resembles its wild type counterpart, the Asn to Asp substitution comprises a hydrogen bonding interaction with a nearby oxygen of the sulfonyl group of GS-6207.

**Conclusion:** Our studies reveal the structural bases for how the HIV-1 CA substitutions confer resistance to the experimental drug GS-6207 and provide the means for rationally developing second-generation inhibitors.

#### 421 GSK3640254 IS A NOVEL MATURATION INHIBITOR WITH AN OPTIMIZED VIROLOGY PROFILE

**Jerry L. Jeffrey**<sup>1</sup>, Mark Cockett<sup>2</sup>, Tricia Protack<sup>3</sup>, Zeyu Lin<sup>3</sup>, Martin Gartland<sup>1</sup>, Ira B. Dicker<sup>2</sup>, Mark Krystal<sup>2</sup>

<sup>1</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>2</sup>ViiV Healthcare, Branford, CT, USA, <sup>3</sup>Bristol Myers Squibb, Redwood City, CA, USA

**Background:** HIV-1 maturation inhibitors (MIs) work late in the replication cycle to block the cleavage of gag p25 into p24 (capsid) and Sp1, resulting in release of noninfectious virions. Previous MIs have demonstrated clinical efficacy but have encountered virologic failures in subjects infected with viruses containing gag polymorphisms such as V362I and the 369-370 region of gag. GSK3640254 (GSK'254) is a new MI with an optimized profile that strongly inhibits viruses containing these polymorphisms.

**Methods:** A medicinal chemistry approach coupled with a virology triage strategy focused on key gag polymorphisms was used to identify GSK'254. The antiviral activity of GSK'254 against select site-directed mutants (SDMs) was compared to a prior maturation inhibitor, GSK3532795 (GSK'795, formerly BMS-986176). Broad spectrum antiviral activity of GSK'254 was also examined against primary isolates across various HIV subtypes and against recombinant viruses with gag genotypes cloned from clinical isolates. In addition, biochemical and resistance studies were used to confirm the mechanism of action (MoA) of GSK'254.

**Results:** Compared to wild-type virus, SDM viruses with gag changes V362I, V370A,  $\Delta$ 370, or R286K/V370A were equally inhibited by GSK'254. The potency of GSK'254 was greater compared to GSK'795 against a panel of 19 primary isolates (subtype A=3, B=7, C=6, CRF01\_AE=3), with a median  $EC_{50}$  of 3 nM (range 1-77 nM) vs. 8 nM for GSK'795 (range 1-1575 nM). Using a panel of 24 Subtype B and 11 Subtype C chimeric viruses with broad gag diversity, GSK'254 exhibited median  $EC_{50}$  values of 1.4 nM (range 0.48-6.9 nM) and 1.4 nM (range 0.85-1.9 nM) for the Subtype B and C viruses, respectively. GSK'254 retained some potency against an A364V SDM ( $EC_{50}$ =143 nM) but exhibited a less than optimal maximal percent inhibition (72.5%) and was selected in resistance studies in cell culture. In vitro MoA studies demonstrated that GSK'254 inhibited cleavage of p25 for consensus subtype B gag as well as gag proteins with relevant SDMs.

**Conclusion:** These data demonstrate the optimized antiviral properties of GSK'254, a once-daily maturation inhibitor, against viruses with common MI-related gag polymorphisms. GSK'254 has been shown to provide significant reduction in viral load in people living with HIV in a phase 2A proof-of-concept study. Together, these data support the ongoing clinical development of GSK'254 in HIV-1 infected individuals

#### 422 REDUCED SUSCEPTIBILITY TO TEMSAVIR IS NOT LINKED TO IBA OR MVC RESISTANCE

**Burt Rose**<sup>1</sup>, Margaret Gartland<sup>2</sup>, Eugene Stewart<sup>3</sup>, Mark Cockett<sup>1</sup>, Peter Ackerman<sup>1</sup>, Max Lataillade<sup>1</sup>, Cyril Llamoso<sup>1</sup>, Mark Krystal<sup>1</sup>

<sup>1</sup>ViiV Healthcare, Branford, CT, USA, <sup>2</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>3</sup>GlaxoSmithKline, Collegeville, PA, USA

**Background:** Tamsavir (TMR), the active agent of the gp120-directed attachment inhibitor fostemsavir (FTR), the CD4-directed attachment inhibitor ibalizumab (IBA) and the CCR5 antagonist maraviroc (MVC) are antiretroviral (ARV) agents that target steps in HIV-1 viral entry. Although the mechanisms of inhibition of the 3 agents are different, it is important to understand whether there is any potential for cross-resistance between these agents since all involve interactions with gp120.

**Methods:** Six envelopes derived from plasma samples from participants in the BRIGHT study who experienced protocol-defined virologic failure (PDVF) and were co-dosed with FTR and either IBA or MVC (3 each) were generated and analyzed for susceptibility to the agents. In addition, 5 R5-tropic MVC-resistant envelopes from the MOTIVATE trials were regenerated based on their gp120 sequences. Site-directed mutagenesis of these envelopes was performed to understand whether susceptibility to multiple agents was linked.

**Results:** The envelopes from participants experiencing PDVF in BRIGHT exhibited reduced susceptibility to TMR and resistance to the co-dosed agent (either IBA or MVC). At PDVF, emergent (compared to baseline) or pre-existing amino acids were present in all envelopes at one or more gp120 positions of interest (375, 426 or 475) that are known to have the potential to adversely affect susceptibility to TMR. When these positions were reverted to the consensus sequence (S375S, M426M or M475M), full susceptibility to TMR was restored in all cases without affecting resistance to the co-dosed agent. In addition, 5 regenerated envelopes from the MOTIVATE studies all exhibited R5-tropic MVC resistance. Only 1 exhibited reduced susceptibility to TMR as it contained an M426L polymorphism. When mutated to L426M, this envelope reverted to full sensitivity for TMR, but remained MVC resistant.

**Conclusion:** Using envelopes obtained from clinical studies, the data clearly show that decreased susceptibility to TMR and resistance to IBA or MVC are not linked and that there is no cross-resistance with these latter 2 agents and FTR.

#### 423 HIV-1 5'-LEADER MUTATIONS IN PWH DEVELOPING RTI-RESISTANCE MUTATIONS

**Janin Nouhin**<sup>1</sup>, Malaya K. Sahoo<sup>1</sup>, Philip L. Tzou<sup>1</sup>, Benjamin A. Pinsky<sup>1</sup>, Joseph D. Puglisi<sup>1</sup>, Elisabetta V. Puglisi<sup>1</sup>, Robert W. Shafer<sup>1</sup>

<sup>1</sup>Stanford University, Stanford, CA, USA

**Background:** RT initiation, which occurs from the 5'-leader region of HIV-1 genomic RNA is a bottleneck to viral replication evidenced by a 50-200-fold reduced rate of nucleotide (NA) incorporation during this phase. We sought to determine whether viruses from PWH receiving RTIs would develop 5'-leader mutations to accommodate the effects of RTI resistance mutations (DRM).

**Methods:** We sequenced paired plasma samples from 36 PWH developing M184VI, 27 PWH developing a major NNRTI DRM, and 34 control untreated PWH with  $\geq 2$  consecutive sequences. Illumina amplicon sequencing encompassed 5'-leader NA positions 37-356 (HXB2:491-810) and RT codons 53-127 and 144-219. In an analysis of baseline sequences, 5'-leader variants were defined as NA differences from the consensus NA present in  $\geq 10\%$  of reads. Shannon's entropy (H) was calculated at each 5'-leader and RT NA position. In an analysis of paired sequences, 5'-leader mutations were defined as NA variants undergoing a  $\geq 4$ -fold change in prevalence between baseline and follow-up.

**Results:** In the baseline sequence analysis, 70% of 5'-leader NA positions were invariant while 30% (n=96) contained  $\geq 1$  variant. Among these 96 positions, 66 (20.6% of the total) contained an NA variant, 12 (3.8%) contained an indel variant, and 18 (5.6%) contained both types of variants. Five 5'-leader positions were more entropic than any RT position: 200 (H=0.56), 201 (H=0.34), 304 (H=0.20), 152 (H=0.17), 305 (H=0.15). In the pairwise sequence analysis, there was no significant difference between the median number of 5'-leader mutations for the 36 PWH developing M184VI (4; IQR:1-7) compared with the 27 developing an NNRTI DRM (2; IQR:0-5.5; p=0.3; Wilcoxon rank sum test) or the 34 control PWH (1.5; IQR:0-6; p=0.1). An analysis of all 5'-leader position found that only 201 (28% vs 3%; p=0.007; Fisher's exact test) and 200 (36% vs 12%; p=0.03), were more likely to mutate in PWH developing M184VI compared with controls (Table 1).

**Conclusion:** Although many regions of the 5'-leader are highly conserved, it is characterized by many indels and several highly entropic positions. The most entropic positions (200 and 201), which lie just downstream of the primer binding site, mutate more often in PWH developing M184VI than in control untreated PWH. This region of HIV-1 genomic RNA is involved in structuring the viral RNA-tRNA<sup>Lys</sup> primer with the RT initiation complex, suggesting how RNA and protein sequence mutations are coupled.

Table 1. Pairwise analysis of 5'-leader sequences from 36 PWH developing M184VI compared with 27 PWH developing an NNRTI DRM and 34 untreated controls

| # mutations per person | M184VI       | NNRTI DRM    |     | Control      |      |
|------------------------|--------------|--------------|-----|--------------|------|
|                        | Median (IQR) | Median (IQR) | P*  | Median (IQR) | P*   |
|                        | 4 (1-7)      | 2 (0-5.5)    | 0.3 | 1.5 (0-6)    | 0.15 |

| Mutation proportion by position | M184VI     | NNRTI DRM  | Control |       |       |
|---------------------------------|------------|------------|---------|-------|-------|
|                                 | Proportion | Proportion | P†      | P†    |       |
| 200                             | 0.36       | 0.30       | NS      | 0.12  | 0.03  |
| 201                             | 0.28       | 0.30       | NS      | 0.03  | 0.007 |
| 305                             | 0.17       | 0.07       | NS      | 0.15  | NS    |
| 304                             | 0.17       | 0.15       | NS      | 0.09  | NS    |
| 152                             | 0.17       | 0.11       | NS      | 0.09  | NS    |
| 96                              | 0.14       | 0.04       | NS      | 0.12  | NS    |
| 265                             | 0.11       | 0.15       | NS      | 0.18  | NS    |
| 227                             | 0.08       | 0.07       | NS      | 0.15  | NS    |
| All other positions             | <0.12      | <0.12      | NS      | <0.12 | NS    |

\*Medians were compared using the Wilcoxon rank sum test. †Proportions were compared using Fisher exact test.

#### 424 MUTATIONS IN GP41 IN PRIMARY HIV-1 ISOLATES CONFER RESISTANCE TO ANTIRETROVIRALS

Yuta Hikichi<sup>1</sup>, Rachel Van Duyn<sup>1</sup>, Phuong Pham<sup>1</sup>, Jennifer L. Groebner<sup>1</sup>, Ann Wiegand<sup>1</sup>, John W. Mellors<sup>2</sup>, Mary F. Kearney<sup>1</sup>, Eric O. Freed<sup>1</sup>

<sup>1</sup>National Cancer Institute, Frederick, MD, USA, <sup>2</sup>University of Pittsburgh, Pittsburgh, PA, USA

**Background:** Although combination antiretroviral (ARV) therapy is able to suppress HIV-1 replication, drug resistance can be a major obstacle to long-term care. In some cases, resistance develops without ARV target-gene mutations. We recently reported that the lab-adapted HIV-1 NL4-3 strain can acquire resistance to the integrase strand transfer inhibitor (INSTI), dolutegravir (DTG) by acquiring mutations in Env that enhance viral cell-cell transmission. The aim of this study is to examine whether Env-mediated drug resistance arises in clinically relevant isolates, and whether Env mutations can confer resistance to other classes of ARVs. Finally, we examined the possibility that Env mutations contribute to drug resistance in vivo.

**Methods:** We propagated clinically relevant HIV-1 strains [subtype B NL(AD8) and subtype C, transmitted founder K3016] in the presence of DTG, rilpivirine and emtricitabine to select variants exhibiting resistance to these drugs. Env mutations that arose were introduced into the wild-type (WT) strain and the replication kinetics and cell-free infectivity in the presence of several ARVs targeting RT, IN, PR and Env were examined. We also performed single-genome sequencing of IN/Env-coding regions of plasma-derived viruses from five individuals failing a raltegravir-containing regimen with therapeutic raltegravir levels in ACTG study A5273.

**Results:** By propagating the NL(AD8) strain in the presence of DTG, we identified the Env-N654K mutation in gp41 heptad repeat 2 (HR2). We also identified Env-T541I (gp41 HR1) and Env-E621V (gp41 disulfide loop region) mutations in the K3016 strain in the presence of DTG and RT inhibitors, respectively. These Env mutants exhibit faster-than-WT replication but reduced cell-free infectivity relative to WT and showed reduced sensitivity to DTG (3.6–30 fold), efavirenz (9.5–23 fold) and nelfinavir (13–25 fold), but not to T-20, in spreading infection. The Env variants did not alter sensitivity to the ARVs in the context of cell-free infection, suggesting that Env mutations reduce sensitivity to ARVs by enhancing the efficiency of cell-cell transmission. We observed mutations in regions of gp41 analogous to those described above in individuals on failing raltegravir-containing ART in the absence of mutations in IN.

**Conclusion:** Our findings suggest that Env-mediated drug resistance may broadly affect HIV sensitivity to ARVs and provide clues towards understanding how ART failure occurs without mutations in drug-target genes.

#### 425 EVALUATION OF bNAb SENSITIVITY BY GENOTYPING AND PHENOTYPING FOR HIV CLINICAL TRIALS

Brian Moldt<sup>1</sup>, PC Parvanga<sup>1</sup>, Ross Martin<sup>1</sup>, Craig Pace<sup>1</sup>, Mini Balakrishnan<sup>1</sup>, Nathan Thomsen<sup>1</sup>, Herbert Kuster<sup>2</sup>, Dominique Braun<sup>2</sup>, Huldrych F. Günthard<sup>2</sup>, Sean E. Collins<sup>1</sup>, Romas Geleziunas<sup>1</sup>, Christian Callebaut<sup>1</sup>

<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>2</sup>University Hospital Zurich, Zurich, Switzerland

**Background:** HIV envelope (Env) diversity is a significant challenge for the use of broadly neutralizing antibodies (bNAbs) in HIV treatment and cure studies. Screening Env for bNAb susceptibility to select sensitive participants will be important to improve clinical efficacy, however, no standard approach has been established. Individuals who initiate ART during primary HIV infection generally have low sequence diversity and are an attractive population for early proof of concept bNAb cure-related trials. We therefore analyzed Env sequences from individuals who started ART during primary HIV infection.

**Methods:** Pre-ART plasma virus from 96 participants in the Zurich Primary HIV Infection Study, who initiated ART during primary HIV infection, was genotyped and phenotyped for susceptibility to the bNAbs elivipimab (EVM, formerly GS-9722) and 3BNC117. The genotypic GenoSure HIV Envelope RNA Assay and the phenotypic PhenoSense HIV nAb Assay assessments were carried out following CLIA guidelines as would be required for entry into clinical trials. For predicting bNAb susceptibility by genotyping, Env amino acid signatures for EVM and 3BNC117 sensitivity were identified from a genotypic-phenotypic correlation algorithm using a subtype B database (n=203 for EVM, N=234 for 3BNC117). A positive predictive value (PPV), was calculated for each genotypic Env signature based on phenotypic sensitivity to the bNAbs.

**Results:** Bioinformatic methods identified Env signatures with PPVs from 75% to 97% for EVM, achieving higher PPVs required more complex Env signatures. Genotyping the plasma virus and applying Env sensitivity signatures with PPVs of 75%, 83%, 91%, 97% identified 57, 32, 25 and 14 participants, respectively, out of 96 as sensitive to EVM. Plasma viruses were also evaluated for sensitivity to EVM by phenotyping. For the 57, 32, 25 and 14 participants predicted to be sensitive by genotyping, 45 (79%), 30 (94%), 23 (92%) and 13 (93%) participants, respectively, were confirmed sensitive to EVM by phenotyping. Similar analyses were performed for 3BNC117.

**Conclusion:** The genotypic assessment using the developed Env signatures for sensitivity appears as predictive as the direct measurement of sensitivity by phenotyping and may therefore be preferred due to turnaround time and assay simplicity. A significant number of the analyzed participants had Env sequences that are susceptible to EVM and 3BNC117 and could thus be potential candidates for trials involving these bNAbs.

#### 426 VARIANT SELECTION, CHARACTERIZATION, AND IMPACT ON ANTIBODY SARS-CoV-2 NEUTRALIZATION

Nicole Kallewaard<sup>1</sup>, Beverly A. Heinz<sup>1</sup>, Robert W. Siegel<sup>1</sup>, Peter Vaillancourt<sup>2</sup>, Bryan E. Jones<sup>2</sup>, Dylan M. Johnson<sup>3</sup>, Viktoriya Borisevich<sup>3</sup>, Thomas W. Geisbert<sup>3</sup>, Robert W. Cross<sup>3</sup>, Andrew C. Adams<sup>1</sup>

<sup>1</sup>Eli Lilly and Company, Indianapolis, IN, USA, <sup>2</sup>Eli Lilly and Company, San Diego, CA, USA, <sup>3</sup>Galveston National Laboratory, University of Texas Medical Branch, Galveston, TX, USA

**Background:** Monitoring genomic variation of SARS-CoV-2 is crucial in mitigating adaptation to the human host and developing effective treatments that safeguard global health. Bamlanivimab and etesevimab are monoclonal antibodies (mAbs) that have demonstrated potent SARS-CoV-2 neutralizing activity in both pre-clinical and clinical settings and have distinct but overlapping binding sites. Here, the selection and characterization of variants in a pre-clinical setting is presented alongside the impact of emerging variants on antibody binding affinity and viral neutralization potency.

**Methods:** Variant selection was carried out via directed evolution of the receptor binding domain (RBD) and serial passage of authentic SARS-CoV-2 in the presence of bamlanivimab and etesevimab individually or in combination. Sequence confirmed, putative-resistance variants identified in both selection methodologies were incorporated into different assessment platforms (VSV-based SARS-CoV-2 pseudovirus neutralization, a yeast RBD display hACE2 competition, and binding affinity to mAb and hACE2) to evaluate potency loss of the selecting mAb and test activity against the mAb combination.

**Results:** Serial passage of SARS-CoV-2 and directed evolution of the RBD protein were unable to select for resistant viral variants under the pressure of mAb combination therapy. In the same experimental paradigm, variants were

identified when each mAb was evaluated alone (E484D/K/Q, F490S, Q493R, and S494P for bamlanivimab and K417N, D420N and N460K/S/T/Y for etesevimab). Neutralization and binding assessments confirmed reduced susceptibility of the variants to the single selecting mAb with 50-fold or greater reductions in potency. Importantly, aside from the Q493R variant, all other resistant viruses were neutralized by the mAb combination therapy.

**Conclusion:** In vitro selection studies using single mAbs, bamlanivimab or etesevimab, identified key positions within the SARS-CoV-2 S-protein that have potential for viral resistance in the clinic, whereas similar studies with the mAb combination therapy were unable to select variants. Binding and competition assays confirmed the neutralization phenotyping data and indicates the mechanism of resistance is due to a reduction in binding affinity. The pre-clinical selection and functional characterization of resistant viral variants directly supports the observation that mAb combination therapy results in a lower frequency of treatment-emergent resistance in clinical treatment studies.

#### 427 MONITORING OF HIV DRUG RESISTANCE AMONG SEROCONVERTERS ON PrEP IN KENYA

**Bhavna Chohan**<sup>1</sup>, Everline Bosek<sup>2</sup>, Irene Mukui<sup>3</sup>, Sarah Masyuko<sup>3</sup>, Mary Mugambi<sup>3</sup>, John Kinuthia<sup>4</sup>, Dorcus Abuya<sup>3</sup>, Barbra A. Richardson<sup>1</sup>, Lisa Levy<sup>5</sup>, Lauren Kudrick-Downey<sup>2</sup>, John W. Mellors<sup>2</sup>, Urvi Parikh<sup>2</sup>  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>3</sup>Ministry of Health, Nairobi, Kenya, <sup>4</sup>Kenyatta National Hospital, Nairobi, Kenya, <sup>5</sup>FHI 360, Washington, DC, USA

**Background:** In 2018, Kenya was the first sub-Saharan African country to nationally implement TDF/FTC PrEP as part of combination prevention in individuals at substantial ongoing risk of HIV infection. Despite high effectiveness, individuals who fail PrEP may risk select resistance to TDF and/or FTC, also used as first-line ART in Kenya. To address this concern, NASCOP and the USAID/PEPFAR-funded GEMS project implemented PrEP resistance monitoring at ~1500 PrEP sites in Kenya and assessed the frequency of HIV drug resistance (HIVDR) mutations among individuals seroconverting after initiating PrEP.

**Methods:** HIVDR monitoring for PrEP seroconverters was implemented through a national protocol that enrolled consenting clients who had access to PrEP. HIVDR content was added to PrEP service provider trainings at county and national levels, and blood collection kits were distributed. Data on sex, age, location, key population, and self-reported PrEP adherence were collected via questionnaire. Blood samples were assessed for resistance using population genotyping at WHO-accredited HIVDR laboratory in Kenya. Resistance mutations were identified using the Stanford HIV Drug Resistance Database.

**Results:** Over 2000 service providers were trained and 340 collection kits distributed nationally. From an estimated 25,000 individuals currently on PrEP, 67 seroconversions were reported, and samples were collected from 55 (82%) clients; of whom 40 (73%) were female, with a median age of 30.5 years [18, 67], and included discordant couples (56%), female sex workers (11%), and men who have sex with men (9%). Eleven (20%) seroconversions occurred within 6 weeks of PrEP initiation; 30 (54%) self-reported adherence as "good" (6-7 PrEP doses/week); and 21 (38%) had HIV-1 RNA <1000 c/ml. Of the 30 successfully genotyped samples, 10 (33%) had major HIVDR mutations detected; precisely, none had K65R or K70E, 5 (17%) had M184V, and 9 (30%) had one or more major NNRTI mutation including K101E, K103N, V106I, G190A, and Y181C.

**Conclusion:** PrEP rollout is highly successful in Kenya, though the number of seroconverters may be underreported despite widespread training and kit dissemination. The rate of PrEP-related resistance with M184I/V (17%) highlights the importance of continued monitoring for HIVDR in PrEP seroconverters to preserve ART options for both treatment and prevention. Additionally, the increased NNRTI resistance suggests transmitted DR warranting continuous monitoring for pretreatment HIVDR among newly infected persons.

#### 428 ULTRASENSITIVE HIV-1 DRUG-RESISTANCE ANALYSIS IN THE DISCOVER PrEP TRIAL

**Stephanie Cox**<sup>1</sup>, Urvi Parikh<sup>2</sup>, Amy Heaps<sup>2</sup>, Jay Goetz<sup>2</sup>, John W. Mellors<sup>2</sup>, Moupali Das<sup>1</sup>, Christian Callebaut<sup>1</sup>  
<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>2</sup>University of Pittsburgh, Pittsburgh, PA, USA

**Background:** The DISCOVER study is an ongoing randomized, double blind study of pre-exposure prophylaxis (PrEP) using daily FTC/TAF (F/TAF; Descovy;

DVY) or FTC/TDF (F/TDF; Truvada; TVD) in men or transgender women who have sex with men. Of the 5,335 randomized participants evaluated for HIV-1 infection, 27 participants (0.5%) became infected with HIV-1 through 144 weeks on study. Participants who acquired HIV were evaluated with population, standard next generation sequencing (NGS), and ultrasensitive sequencing and the overall resistance data and analysis are presented here.

**Methods:** Plasma samples from participants who became infected with HIV-1 and had a viral load of > 400 copies/mL were tested with the GenoSure™ MG assay (Monogram) to analyze the protease (PR) and reverse transcriptase (RT) genes for resistance associated mutations (RAMs) (at ≥15-20% of the viral population). Additional analysis of the PR-RT and integrase (IN) genes on all available plasma samples was performed by standard NGS (SeqIT) to evaluate resistance mutations (at ≥2% of the viral population). Ultrasensitive resistance testing was done using unique molecular identifiers for amplification of viral variants (at ≥1% of the viral population) followed by NGS (UMI-NGS), to analyze RT codons 63-131 and 152-211 (University of Pittsburgh).

**Results:** By population sequencing, 4/20 participants infected with HIV had M184V, all in the F/TDF group and all with suspected baseline infection; 2 of these 4 also had M184I present. By standard NGS and UMI-NGS, 26/27 HIV participants infected with HIV had samples available and 25/27 were successfully analyzed. For the 4 participants on F/TDF with M184V, each had M184I also detected. By UMI-NGS, 1 participant on F/TAF had the M184V mutation present at 2%. Ten participants had additional mutations conferring resistance to non-study drugs including INSTI RAMs T66A, E92G, Y143C, Q148R, N155H; PI RAMs M46I; NNRTI RAMs V90I, V106I, K103N, Y188L, which were presumed to be transmitted.

**Conclusion:** Using population sequencing and standard NGS, M184V was detected in 4 participants, all in the F/TDF arm. With ultrasensitive UMI-NGS testing, similar results were observed in the F/TDF arm, with the addition of 1 participant with M184V in the F/TAF arm. In addition, analysis by standard NGS of the PR, RT and IN genes found notable transmitted drug resistance to non-study drugs. Overall, resistance to study drugs in the DISCOVER study was infrequently seen and primarily with suspected baseline infections.

#### 429 IMPACT OF M184V ON THE VIROLOGICAL EFFICACY OF SWITCH TO 3TC/DTG IN REAL LIFE

**Maria M. Santoro**<sup>1</sup>, Daniele Armenia<sup>2</sup>, Elisa Teyssou<sup>3</sup>, José Ramón Santos<sup>4</sup>, Charlotte Charpentier<sup>5</sup>, Sidonie Lambert-Niclot<sup>6</sup>, Andrea Antinori<sup>7</sup>, Christine Katlama<sup>3</sup>, Diane Descamps<sup>5</sup>, Carlo F. Perno<sup>8</sup>, Vincent Calvez<sup>2</sup>, Roger Paredes<sup>4</sup>, Francesca Ceccherini-Silberstein<sup>1</sup>, Anne Genevieve Marcelin<sup>3</sup>, for the LAMRES Study Group

<sup>1</sup>University of Rome Tor Vergata, Rome, Italy, <sup>2</sup>Saint Camillus International University of Health Sciences, Rome, Italy, <sup>3</sup>Hôpital Pitié-Salpêtrière, Paris, France, <sup>4</sup>Hospital Germans Trias i Pujol, Barcelona, Spain, <sup>5</sup>Hôpital Bichat-Claude-Bernard, Paris, France, <sup>6</sup>Saint-Antoine Hospital, Paris, France, <sup>7</sup>National Institute for Infectious Diseases "L. Spallanzani", IRCCS, Rome, Italy, <sup>8</sup>Bambino Gesù Children's Hospital, Rome, Italy

**Background:** The impact of previous selection of M184V on virological response to 3TC/DTG in real life is still unclear. The aim of this study was to assess the efficacy of 3TC/DTG in a large set of virologically suppressed patients with or without past M184V.

**Methods:** In this European retrospective study, individuals with plasma HIV-RNA ≤50 cps/mL who switched to 3TC/DTG and with at least 1 previous HIV-RNA or HIV-DNA genotype before switch were included. Survival analysis was used to evaluate the role of past M184V on experiencing a virological failure (VF: HIV-RNA >50 cps/mL in 2 consecutive determinations or ≥200 cps/mL in a single determination) or a blip (a single HIV-RNA in the range 51-199 cps/mL preceded and followed by ≤50 cps/mL measurements) after 3TC/DTG switch. Resistance at VF was also evaluated.

**Results:** Results: 533 individuals followed in several clinical centers in France, Italy and Spain were analyzed: 79.2% were male, with a median (IQR) age of 51 (43-58) yrs; median (IQR) time of virological suppression was 5.4 (2.7-9.5) yrs; median (IQR) number of previous VFs was 0 (0-1); median time under 3TC/DTG was 22 (17-39) months. Past M184V was present in 37 (6.9%) individuals. Median (IQR) time of last detection of M184V before 3TC/DTG switch was 11 (5-15) yrs. By stratifying for the presence/absence of M184V, no significant difference in the probability of VF was found (5.4% vs 2.6% at 1 yr and 9.2% vs 4.4% at 2 yr; p=0.345). However, a significant higher probability of VF was found in individuals with M184V detected ≤5 yrs before 3TC/DTG

switch compared to those in whom M184V was detected >5 yrs and those without M184V, at both 1 yr (20% vs 0% vs 2.6%) and 2 yrs (20% vs 5% vs 4.4%; p=0.007) after switch. This finding was confirmed by multivariable Cox regression (Table). Other factors associated with VF were risk factor, zenith viremia and previous resistance to at least 3 classes. The probability of experiencing blips was 3.6% and 7.3% at 1 and 2 yrs, without any statistical significance in the 2 groups considered (p=0.321), neither after considering the time of last M184V detection (p=0.596). Genotypic resistance test was available for 4/22 individuals who failed 3TC/DTG; no resistance to INIs and NRTIs was found.

**Conclusion:** In this real life study, the probability of VF in patients switching to 3TC/DTG is very low after 2 yrs of treatment. Past M184V influenced VF only in the context of a more "recent" (<5 years) detection. Larger data are necessary to support this result.

that preexisting TDR did not affect treatment outcomes. One participant had preexisting Q148H+G140S in IN and K70R and K103N in RT at baseline. This participant was randomized to B/F/TAF, had HIV-1 RNA <50 copies/mL at Week 4, and maintained HIV-1 RNA <50 copies/mL through Week 144. In total, 21 participants qualified for post-baseline resistance testing (1.3% [8/634] B/F/TAF; 1.9% [6/315] DTG/ABC/3TC; 2.2% [7/325] DTG+F/TAF); of those, 2/8 B/F/TAF, 6/6 DTG/ABC/3TC, and 4/7 DTG+F/TAF participants had multiple confirmed virologic rebounds during the studies. No participant had emergent resistance to study drugs.

**Conclusion:** Initial HIV-1 treatment with B/F/TAF, DTG/ABC/3TC, or DTG+F/TAF achieved high, durable rates of virologic suppression. The presence of TDR did not affect treatment outcomes, and there was no treatment-emergent resistance through 144 weeks.

Table. Patients' characteristics and factors associated with viral blips or virological failure in 533 virologically suppressed individuals who switched for the first-time to 3TC/DTG

| Variables  | Overall (N=533) | Hazard ratios for experience viral blips |                  |                        | Hazard ratios for experience virological failure |                  |                        |
|--|-----------------|--|------------------|------------------------|--|------------------|------------------------|
|  |                 | Crude HR (95% C.I.)                      | Adjusted P Value | Adjusted HR (95% C.I.) | Crude HR (95% C.I.)                              | Adjusted P Value | Adjusted HR (95% C.I.) |
| <b>Male, n (%)</b>                                       | 422 (79.2)      | 1.0 (0.5-2.1)                            | 0.892            | 0.3 (0.1-0.7)          | 0.003  | 0.5 (0.2-1.3)    | 0.155                  |
| <b>Risk factor, n (%)</b>                                | 252 (47.3)      | 1  |                  | 1                      |  | 1                |                        |
| Heterosexual   | 169 (31.7)      | 2.1 (1.4-3.3)                            | 0.039            | 2.1 (1.4-3.3)          | 0.052  | 4.8 (3.1-7.3)    | 0.002                  |
| Drug abuser  | 62 (11.6)       | 3.1 (1.6-6.9)                            | 0.006            | 2.9 (1.2-7.1)          | 0.020  | 2.2 (0.5-9.1)    | 0.290                  |
| Sexual   | 27 (5.1)        | 1.7 (0.7-3.7)                            | 0.202            | 1.6 (0.7-3.7)          | 0.232  | 2.2 (0.3-16.8)   | 0.479                  |
| Other/injection  | 27 (5.1)        | 1.4 (0.3-6.1)                            | 0.668            | 0.9 (0.2-4.4)          | 0.946  | 0.0 (0.0-0.0)    | 0.978                  |
| <b>Emicity, n (%)</b>                                    | 391 (73.4)      | 1  |                  | 1                      |  | 1                |                        |
| Caucasian  | 23 (4.3)        | 0.5 (0.1-3.3)                            | 0.440            | 2.1 (0.5-9.2)          | 0.311  | 0.7 (0.1-3.6)    | 0.646                  |
| Hispanic   | 18 (3.4)        | 0.0 (0.0-0.0)                            | 0.971            | 4.1 (2.1-8.6)          | 0.027  | 3.9 (0.3-56.3)   | 0.055                  |
| Other/injection  | 161 (30.9)      | 0.7 (0.2-1.4)                            | 0.315            | 0.6 (0.2-2.2)          | 0.491  | 0.4 (0.1-1.2)    | 0.272                  |
| <b>Adherence, n (%)</b>                                  | 139 (26.4)      | 1  |                  | 1                      |  | 1                |                        |
| High   | 22 (4.1)        | 2.1 (0.8-5.1)                            | 0.130            | 5.1 (1.6-16.9)         | 0.003  | 2.3 (0.4-12.8)   | 0.356                  |
| Medium/Low   | 381 (71.5)      | 1.5 (0.7-3.2)                            | 0.248            | 1.7 (0.8-3.9)          | 0.344  | 1.1 (0.4-3.7)    | 0.895                  |
| <b>Time of previous virological suppression, n (%)</b>   | 52 (9.8)        | 1  |                  | 1                      |  | 1                |                        |
| <1 year  | 52 (17.3)       | 1.3 (0.5-3.7)                            | 0.620            | 0.3 (0.1-1.0)          | 0.057  | 0.5 (0.1-1.7)    | 0.213                  |
| 1-3 years  | 50 (17.4)       | 0.6 (0.2-1.9)                            | 0.368            | 0.3 (0.1-1.0)          | 0.046  | 0.4 (0.1-0.8)    | 0.240                  |
| 3-5 years  | 157 (29.5)      | 1.6 (0.4-7.2)                            | 0.576            | 0.3 (0.1-0.8)          | 0.014  | 0.5 (0.2-1.7)    | 0.268                  |
| >5 years   | 102 (22.1)      | 0.6 (0.2-1.7)                            | 0.352            | 0.2 (0.0-0.8)          | 0.016  | 0.2 (0.1-0.3)    | 0.106                  |
| Unknown  | 16 (3.0)        | 0.0 (0.0-0.1)                            | 0.967            | 0.0 (0.0-0.0)          | 0.980  | 1.0 (0.0-0.0)    | 0.994                  |
| <b>Number of viral blips before switch, median (IQR)</b> | 0 (0-1)         | 1.3 (0.1-1.7)                            | 0.022            | 1.1 (0.5-1.5)          | 0.313  | 1 (0.5-1)        | 0.795                  |
| <b>Viremia (Zml copies/mL), n (%)</b>                    | 225 (42.2)      | 1  |                  | 1                      |  | 1                |                        |
| <100,000   | 189 (31.5)      | 1.7 (0.8-3.3)                            | 0.140            | 2.6 (0.8-9.1)          | 0.063  | 3.3 (0.1-11.1)   | 0.050                  |
| 100,000-500,000  | 111 (20.8)      | 1.7 (0.8-3.3)                            | 0.164            | 4.1 (1.4-12.0)         | 0.009  | 3.6 (1.1-12.0)   | 0.041                  |
| >500,000   | 29 (5.4)        | 0.5 (0.1-3.6)                            | 0.457            | 0.0 (0.0-0.0)          | 0.975  | 0.0 (0.0-0.0)    | 0.994                  |
| <b>Target not detected at switch, n (%)</b>              | 232 (43.5)      | 1  |                  | 1                      |  | 1                |                        |
| No   | 266 (49.9)      | 0.5 (0.3-0.9)                            | 0.016            | 0.4 (0.2-0.7)          | 0.002  | 0.5 (0.2-1.0)    | 0.062                  |
| Yes  | 36 (6.6)        | 0.2 (0.1-1.7)                            | 0.154            | 0.3 (0.0-2.0)          | 0.200  | 0.0 (0.0-0.0)    | 0.980                  |
| Unknown  | 209 (39.2)      | 2.0 (1.3-3.3)                            | 0.004            | 1.7 (0.9-3.3)          | 0.098  | 1.8 (0.8-4.0)    | 0.135                  |
| <b>At least one failure before switch, n (%)</b>         | 19 (3.4)        | 1.6 (0.5-5.8)                            | 0.326            | 4.0 (2.1-7.4)          | 0.024  | 2.4 (0.5-11.2)   | 0.253                  |
| <b>Int. failure before switch, n (%)</b>                 | 403 (75.6)      | 1  |                  | 1                      |  | 1                |                        |
| None   | 91 (17.1)       | 1.0 (0.4-2.3)                            | 0.990            | 0.8 (0.3-1.8)          | 0.537  | 1.6 (0.6-4.4)    | 0.366                  |
| 1  | 28 (5.3)        | 1.6 (0.6-4.6)                            | 0.353            | 0.8 (0.3-2.3)          | 0.659  | 3.0 (0.8-10.3)   | 0.089                  |
| 2  | 11 (2.1)        | 4.9 (1.7-14.0)                           | 0.003            | 3.1 (1.0-9.9)          | 0.052  | 7.1 (2.2-23.7)   | 0.002                  |
| ≥3   | 486 (93.1)      | 1.5 (0.6-3.9)                            | 0.380            | 1.8 (0.5-5.9)          | 0.352  | 1.8 (0.5-5.9)    | 0.352                  |
| <b>Past M184V, n (%)</b>                                 | 486 (93.1)      | 1  |                  | 1                      |  | 1                |                        |
| Never detected   | 16 (3.0)        | 1.2 (0.2-6.9)                            | 0.851            | 5.6 (1.3-23.7)         | 0.020  | 1.9 (0.2-14.0)   | 0.518                  |
| detected <5 years before switch                          | 27 (5.1)        | 1.6 (0.6-4.5)                            | 0.359            | 0.7 (0.1-5.6)          | 0.778  | 0.6 (0.0-0.2)    | 0.040                  |
| detected >5 years before switch                          | 466 (93.1)      | 1.0 (0.4-2.3)                            | 0.990            | 0.8 (0.3-1.8)          | 0.537  | 1.6 (0.6-4.4)    | 0.366                  |

The following variables have been considered for the Cox regression analysis: sex, age, risk factor, ethnicity, HIV-1 subtype, adherence, time of previous virological suppression before 3TC/DTG switch, number of previous viral blips before 3TC/DTG switch, nadir CD4 cell count, CD4 cell count at 3TC/DTG switch, time under ART before 3TC/DTG switch, 3TC/DTG switch after first-line regimen, at least one virological failure before 3TC/DTG switch, 3TC/DTG switch class resistance accumulated before 3TC/DTG switch among PI, NRTI, NNRTI and INSTI, presence/absence of past M184V, last detection time of M184V before 3TC/DTG switch, percentage of individuals with viremia target not detected (TND) at 3TC/DTG switch. In the table are reported variables that were significant in at least one univariable model and the presence/absence of past M184V. Multi-variable models were built by considering only variables that were significant (p<0.05) in the univariable model. Acronyms: RT: integrase inhibitor; not: not determined; \*Detection of past M184V only in HIV-RNA; n/25: only in HIV-QNA; n/7: only in HIV-QNA and HIV-QNA; n/1: only in HIV-QNA.

Table. Transmitted Drug Resistance Substitutions and Impact on Treatment Outcome

| Resistance Substitutions at Baseline | HIV-1 RNA <50 copies/mL at Week 144, n/N (%) <sup>a</sup> |                            |                          |
|--------------------------------------|---|----------------------------|--------------------------|
|                                      | B/F/TAF 1489, 1490 (N = 624)                              | DTG/ABC/3TC 1489 (N = 315) | DTG+F/TAF 1490 (N = 325) |
| <b>Any TDR</b>                       |   |                            |                          |
| Yes                                  | 112/113 (99.1)  | 68/71 (95.8)               | 62/63 (98.4)             |
| No                                   | 504/514 (98.1)  | 234/243 (96.3)             | 253/262 (96.6)           |
| <b>Primary NRTI-associated</b>       |   |                            |                          |
| Yes                                  | 21/21 (100)   | 8/8 (100)                  | 6/6 (100)                |
| No                                   | 595/606 (98.2)  | 294/306 (96.1)             | 309/319 (96.9)           |
| <b>Primary INSTI-associated</b>      |   |                            |                          |
| Yes                                  | 7/7 (100)   | 3/4 (75.0)                 | 6/6 (100)                |
| No                                   | 608/620 (98.1)  | 299/310 (96.5)             | 308/319 (96.6)           |
| <b>Primary NNRTI-associated</b>      |   |                            |                          |
| Yes                                  | 81/82 (98.8)  | 52/53 (98.1)               | 44/45 (97.8)             |
| No                                   | 535/545 (98.2)  | 250/261 (95.8)             | 271/280 (96.8)           |
| <b>Primary PI-associated</b>         |   |                            |                          |
| Yes                                  | 18/18 (100)   | 12/13 (92.3)               | 12/12 (100)              |
| No                                   | 598/609 (98.2)  | 290/301 (96.3)             | 303/313 (96.8)           |

a. The LOCF outcome analysis did not include 7 B/F/TAF participants and 1 DTG/ABC/3TC participant who had no on-treatment post-baseline HIV-1 RNA data. 1 of these B/F/TAF participants had a primary PI-associated resistance substitution.

431 DRUG RESISTANCE DURING LOW-LEVEL HIV VIREMIA SUPPORTS LOWERING THRESHOLD FOR SWITCH

Jennifer A. Brown<sup>1</sup>, Alain Amstutz<sup>1</sup>, Bienvenu L. Nsakala<sup>2</sup>, Ulrike Seeburg<sup>3</sup>, Fiona Vanobberghen<sup>1</sup>, Josephine Muhairwe<sup>2</sup>, Thomas Klimkait<sup>3</sup>, Niklaus D. Labhardt<sup>1</sup>

<sup>1</sup>Swiss Tropical and Public Health Institute, Basel, Switzerland, <sup>2</sup>SolidarMed, Maseru, Lesotho, <sup>3</sup>University of Basel, Basel, Switzerland

**Background:** The World Health Organization (WHO) guidelines on antiretroviral therapy (ART) define the HIV-1 viral load (VL) threshold for treatment failure as 1,000 copies/mL. The SESOTHO trial, conducted in Lesotho, found that patients with persistent viremia below this threshold on first-line ART benefitted from switching to second-line ART. This pre-planned nested study assessed the prevalence of resistance-associated mutations (RAMs) in SESOTHO trial participants.

**Methods:** From August 1, 2017 until August 7, 2019, the SESOTHO trial enrolled 80 persons taking non-nucleoside reverse transcriptase inhibitor (NNRTI; efavirenz or nevirapine)-based first-line ART with low-level HIV-1 viremia (100-999 copies/mL). Participants were randomised (1:1) to either switch to a protease inhibitor (PI)-based second-line regimen (switch) or continue on first-line therapy as per the WHO standard of care (control). We sequenced relevant regions of the viral pol gene using plasma samples obtained at enrolment and the 36-week follow-up. RAMs and levels of drug resistance were classified according to the Stanford HIV drug resistance database.

**Results:** Overall, 49/80 (61%) participants had resistance data available at enrolment and/or 36 weeks. 34/49 (69%) were female, the median age was 41 years (IQR 32-50), and median time on ART was 7.3 years (IQR 4.4-8.9). The proportion of participants harbouring nucleoside reverse transcriptase inhibitor (NRTI) and NNRTI resistance (at one or both time points) was 41/49 (84%) and 42/49 (86%), respectively. Considering each time point individually, sequencing was successful for 37/80 (46%) participants at baseline and 26/48 (54%) participants without viral suppression to <50 copies/mL at 36 weeks (21 control; 5 switch). At baseline, 31/37 (84%) participants harboured HIV with high-level resistance to ≥2 drugs of their pre-enrolment regimen. At 36 weeks, 17/21 (81%) control arm participants harboured HIV with resistance to ≥2 drugs of their current (first-line) regimen, while no PI-associated resistance was detected in the five switch (second-line) participants.

**Conclusion:** Among persons with low-level viremia while taking NNRTI-based first-line ART enrolled in the SESOTHO trial, the majority harboured HIV-1 with RAMs that necessitated ART modification. These findings support lowering the VL threshold that triggers a switch to second-line ART in future WHO guidelines.

430 HIV WITH TRANSMITTED DRUG RESISTANCE IS DURABLY SUPPRESSED BY B/F/TAF AT WEEK 144

Rima K. Acosta<sup>1</sup>, Grace Q. Chen<sup>1</sup>, Silvia Chang<sup>1</sup>, Ross Martin<sup>1</sup>, Xinxin Wang<sup>1</sup>, Hailin Huang<sup>1</sup>, Diana Brainard<sup>1</sup>, Jason Hindman<sup>1</sup>, Sean E. Collins<sup>1</sup>, Hal Martin<sup>1</sup>, Kirsten L. White<sup>1</sup>

<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** Two phase 3, randomized, double-blind, active-controlled studies of initial HIV-1 treatment demonstrated that bicitegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) was non-inferior to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC, Study 1489) or to DTG+F/TAF (Study 1490) through 144 weeks. In both studies, there was no emergent resistance to study drugs. Here, we describe the effect of baseline transmitted drug resistance (TDR) on treatment response over 3 years.

**Methods:** Population sequencing of HIV-1 protease and reverse transcriptase (RT) was performed at screening; resistance to study nucleos(t)ide reverse transcriptase inhibitors (NRTIs) was excluded. Retrospective baseline next generation sequencing of protease, RT, and integrase (IN) was analyzed at a ≥15% cutoff. Treatment outcomes were assessed at Week 144 using last on-treatment observation carried forward (LOCF). Resistance analyses were performed on participants with confirmed viral rebound of HIV-1 RNA ≥200 copies/mL through Week 144 or last visit who did not resuppress to <50 copies/mL while on study drug.

**Results:** Of 1421 PLWH screened for both studies, only 3 (0.2%) were excluded due to TDR to FTC, TAF, ABC, or 3TC. TDR was present in 19.5% (248/1274) of enrolled participants and consisted of INSTI resistance (-R) in 1.3% (17/1270 with data), NRTI-R in 2.7% (35/1274), NNRTI-R in 14.1% (179/1274), and PI-R in 3.5% (44/1274). Treatment outcomes by LOCF at Week 144 of participants with or without TDR were comparable (98% of those with primary TDR had HIV RNA <50 copies/mL vs. 97% of those without TDR) (Table), indicating

| SESOTHO trial population   | Control arm (n=40)      | Switch arm (n=40)       | Total (n=80)             |
|--|-------------------------|-------------------------|--------------------------|
| Available HIV sequences at enrollment  | N=16                    | N=21                    | N=37                     |
| Last VL before enrolment in copies/mL, median (IQR) [range]  | 399 (215-761) [167-897] | 486 (122-723) [109-950] | 425 (200-723) [109-950]  |
| 3 first-line ARVs predicted fully active   | 4/16 (25%)              | 2/21 (10%)              | 6/37 (16%)               |
| 1 first-line ARV predicted fully active  | 1/16 (6%)               | 3/21 (14%)              | 4/37 (11%)               |
| No first-line ARVs predicted fully active  | 11/16 (69%)             | 16/21 (76%)             | 27/37 (73%)              |
| Available HIV sequences at 36 weeks  | N=21                    | N=5                     | N=26                     |
| VL, copies/mL, median (IQR) [range]  | 568 (269-986) [58-9560] | 1170 (162-3330) [7040]  | 612 (162-1170) [58-9560] |
| 3 ARVs predicted fully active  | 2/21 (10%)              | 4/5 (80%)               | 6/26 (23%)               |
| 2 ARVs predicted fully active <sup>a</sup>   | 2/21 (10%)              | 1/5 (20%)               | 3/26 (12%)               |
| <i>(including one control and one switch arm participant with incomplete sequencing of the reverse transcriptase only covering codons 1-154)</i> |                         |                         |                          |
| 1 ARV predicted fully active   | 2/21 (10%)              | 0                       | 2/26 (8%)                |
| No active ARVs   | 15/21 (71%)             | 0                       | 15/26 (58%)              |

#### 432 EVALUATION OF COMBINATIONS OF CLINICAL INTEGRASE MUTATIONS ON InSTI RESISTANCE

Peter K. Cheung<sup>1</sup>, Aniqah Shahid<sup>2</sup>, Winnie K. Dong<sup>1</sup>, Katherine J. Lepik<sup>3</sup>, Mark A. Brockman<sup>2</sup>, Zabrina L. Brumme<sup>1</sup>, Chanson Brumme<sup>1</sup>

<sup>1</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, <sup>2</sup>Simon Fraser University, Burnaby, Canada, <sup>3</sup>St Paul's Hospital, Vancouver, Canada

**Background:** While major integrase strand transfer inhibitor (InSTI) resistance mutations have been identified, the effect of mutation combinations on phenotypic resistance are less clear. We identified a clinical HIV sequence with four major integrase resistance mutations, and characterized in vitro InSTI phenotypic susceptibility of all combinations thereof to deconstruct their individual and combined effects.

**Methods:** Routine clinical testing identified an integrase sequence harboring T97A, E138K, G140S and Q148H. We constructed chimeric NL4-3 viruses harboring i) all 15 combinations of these mutations in the autologous integrase backbone, ii) the autologous sequence with these four sites "reverted" to consensus B residues and iii) NL4-3 with all four mutations. Chimeric viruses were grown in a reporter CD4+ T-cell line in the presence of 0.01-1,000nM raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), cabotegravir (CAB), and bictegravir (BIC), where infection was measured by imaging cytometry.

**Results:** Consistent with the known fitness impact of Q148H and its compensation by G140S, viruses engineered with Q148H without G140S either failed to propagate, or propagated only after in vitro mutation; these were excluded from analysis. In the autologous viral backbone, T97A, E138K, or G140S alone conferred 2.4 to 15.4-fold decreased susceptibility to EVG but not to other InSTI (Table 1). Two-mutation combinations conferred low to moderate resistance, except G140S/Q148H which eliminated RAL and EVG activity and conferred 8.3-, 50.9-, and 3.1-fold reduced susceptibility to DTG, CAB, and BIC respectively. Addition of E138K to G140S/Q148H conferred 12.1, 98.6 and 4.6-fold less susceptibility to DTG, CAB, and BIC respectively, while addition of T97A to G140S/Q148H conferred >100-, >100 and 47.7-fold reduced susceptibility to these drugs. The T97A/E138K/G140S/Q148H clinical sequence displayed >100-fold reduced susceptibility to all InSTIs. The quadruple NL4.3 mutant displayed >100-fold less susceptibility to RAL, EVG and CAB but only 66.2-, and 8.2-fold less to DTG, and BIC respectively, while the clinical revertant retained 2.8-fold decreased susceptibility to EVG. Together this suggests that the autologous clinical backbone also contributed to resistance. Measured EC<sub>50</sub>s correlated strongly with Stanford HIVdb resistance scores (Spearman r>0.87; p<0.0001 for all InSTIs).

**Conclusion:** High-level resistance to DTG, CAB and BIC requires multiple integrase substitutions including compensatory mutations.

| Integrase Backbone | Mutation Profile       | RAL                         | EVG                         | DTG                         | CAB                         | BIC                         |
|--------------------|------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                    |                        | EC <sub>50</sub> FC (95%CI) |
| Autologous         | E138K                  | 0.4 (0.2-0.6)               | 2.4 (1.1-5.3)               | 0.2 (0.1-0.2)               | 0.3 (0.2-0.8)               | 0.2 (0.1-0.4)               |
| Autologous         | T97A                   | 1.6 (0.7-3.4)               | 14.0 (6.9-28.4)             | 0.1 (0.1-0.2)               | 0.2 (0.2-0.3)               | 0.1 (0.1-0.2)               |
| Autologous         | G140S                  | 1.3 (0.7-2.7)               | 15.4 (5.3-44.7)             | 0.3 (0.1-0.6)               | 0.5 (0.3-0.8)               | 0.3 (0.1-0.6)               |
| Autologous         | E138K_G140S            | 3.2 (1.8-5.5)               | 16.9 (8.1-35.2)             | 0.4 (0.3-0.7)               | 0.8 (0.4-1.8)               | 0.3 (0.2-0.4)               |
| Autologous         | T97A_E138K             | 4.5 (1.7-11.6)              | 20.1 (11.0-36.5)            | 0.3 (0.2-0.5)               | 0.5 (0.3-1.0)               | 0.2 (0.1-0.4)               |
| Autologous         | T97A_G140S             | 13.1 (7.1-24.1)             | 21.8 (11.6-40.8)            | 0.9 (0.6-1.3)               | 3.5 (1.7-7.2)               | 0.8 (0.5-1.3)               |
| Autologous         | G140S_Q148H            | >1000                       | >1000                       | 8.3 (4.6-15.1)              | 50.9 (24.3-106.8)           | 3.1 (1.9-5.1)               |
| Autologous         | T97A_E138K_G140S       | 35.5 (17.5-72.4)            | 58.8 (36.6-94.2)            | 2.2 (1.0-3.2)               | 6.1 (4.0-9.3)               | 2.0 (1.4-2.9)               |
| Autologous         | E138K_G140S_Q148H      | >1000                       | >1000                       | 12.1 (5.7-25.4)             | 98.6 (40.8-238.2)           | 4.6 (1.9-11.0)              |
| Autologous         | T97A_G140S_Q148H       | >1000                       | >1000                       | 107.9 (52.5-221.7)          | 498.6 (139.2-1786.0)        | 47.7 (16.1-140.6)           |
| Autologous         | T97A_E138K_G140S_Q148H | >1000                       | >1000                       | 153.8 (77.2-306.7)          | 817.9 (162.4-4118.4)        | 120.1 (45.5-317.0)          |
| HIV-1NL4.3         | T97A_E138K_G140S_Q148H | >1000                       | >1000                       | 66.2 (23.2-188.8)           | 288.6 (98.8-723.4)          | 8.2 (3.5-19.3)              |
| Autologous         | Clinical Revertant     | 0.4 (0.2-0.6)               | 2.8 (1.5-5.1)               | 0.3 (0.2-0.6)               | 0.5 (0.3-0.7)               | 0.4 (0.2-0.7)               |
| HIV-1NL4.3         | NL4.3WT                | 1.0                         | 1.0                         | 1.0                         | 1.0                         | 1.0                         |

#### 433 PUBLIC AVAILABILITY OF HIV POL SEQUENCES AND ART HISTORIES IN ACQUIRED HIVDR STUDIES

Soo-Yon Rhee<sup>1</sup>, Michael R. Jordan<sup>2</sup>, Seble Kassaye<sup>3</sup>, Vinie Kouamou<sup>4</sup>, David Katzenstein<sup>4</sup>, Robert W. Shafer<sup>1</sup>

<sup>1</sup>Stanford University, Stanford, CA, USA, <sup>2</sup>Tufts University, Boston, MA, USA, <sup>3</sup>Georgetown University, Washington, DC, USA, <sup>4</sup>University of Zimbabwe, Harare, Zimbabwe

**Background:** The public availability of HIV-1 pol sequences from PWH with viral failure (VF) on ART make it possible to fully define the epidemiology of acquired HIV drug resistance (HIVDR), and the extent of ART cross-resistance associated with specific ART regimens. We therefore sought to determine how often the sequences and linked ART histories from published papers of acquired HIVDR are made publicly available.

**Methods:** We performed a systematic review of studies in PubMed since 2010 describing pol sequences from ≥25 adult PWH with VF on ART. Studies with median sequence year was before 2007 were excluded. Studies of previously PI-naïve PWH receiving atazanavir/r or darunavir/r, previously NNRTI-naïve PWH receiving rilpivirine or doravirine, and previously InSTI-naïve persons receiving dolutegravir were included even if they included fewer than 25 PWH.

**Results:** 351 published studies met inclusion criteria including (i) 124 studies of WHO 1st-line NNRTI (NVP/EFV)-containing regimen; (ii) 53 studies of a PI-containing regimen; (iii) 7 studies of a 2nd-generation NNRTI; (iv) 32 studies of an InSTI-containing regimen; (v) 20 studies containing mixtures of PWH receiving the preceding types of ART; and (vi) 115 studies of uncertain or complicated ART regimens not conforming to the preceding categories. Sequences from 163 studies (46.4%) were publicly available in GenBank, and 71 (20.2%) had linked ART histories in the Stanford HIV Drug Resistance Database. Of 45 clinical trials, sequences were available for 11 (24.4%) and sequences plus linked ART histories were available for 6 (13.3%). Among the 18 journals publishing ≥10 studies, the proportions of studies with publicly available sequences ranged from 10% to 87%. There was no significant temporal increase in the proportion of studies with publicly available sequences (OR: 0.98; 95% CI: 0.93-1.03; p=0.4).

**Conclusion:** Among 351 recently published studies of sequence data from ART-experienced PWH, sequences were available for less than half of the studies and less than a quarter had linked sequences plus ART histories available. Further increases in data sharing are required to fully define the genetic correlates and epidemiology of acquired HIVDR globally. This information in return is critical to the development of ART guidelines in regions where resistance testing is not routinely available.

#### 434 ANALYSIS OF INTRAHOST Gag-Pol EVOLUTION WITH NOVEL SINGLE-MOLECULE SEQUENCING METHOD

Christian M. Gallardo<sup>1</sup>, Shiyi Wang<sup>1</sup>, Daniel J. Montiel-Garcia<sup>2</sup>, Susan J. Little<sup>3</sup>, Davey M. Smith<sup>3</sup>, Andrew L. Routh<sup>4</sup>, Bruce E. Torbett<sup>1</sup>

<sup>1</sup>Seattle Children's Research Institute, Seattle, WA, USA, <sup>2</sup>The Scripps Research Institute, La Jolla, CA, USA, <sup>3</sup>University of California San Diego, San Diego, CA, USA, <sup>4</sup>The University of Texas Medical Branch, Galveston, TX, USA

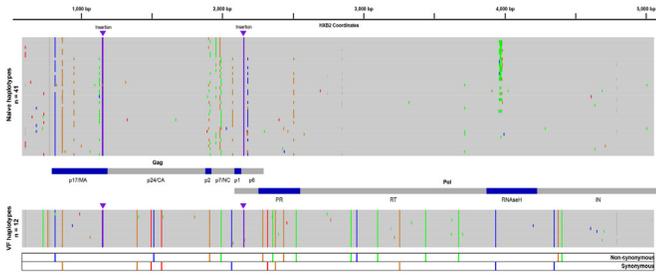
**Background:** Technical challenges remain in the sequencing of circulating HIV vRNA due to its high intrahost diversity. This bottleneck is particularly pronounced when interrogating long-range co-evolution, which has hampered the direct observation of genetic interactions that code for protein-protein interfaces with relevance in drug and vaccine development. To overcome the read-length limitations of NGS and the problematic error rates of long-read sequencing platforms, we developed MrHAMER, a nanopore-based long-read viral sequencing pipeline that yields thousands of accurate Gag-Pol sequences from individual circulating virions in clinical samples.

**Methods:** MrHAMER uses concatenated sense/antisense repeats of each 5kb Gag-Pol cDNA (derived from single RNA molecules) to reduce Nanopore long-read sequencing error from 10% to 0.1%. This end-to-end pipeline is extensively validated for HIV vRNA sequencing of clinical samples containing low input amounts (as few as 2,500 copies/mL). This includes development of a novel emulsion-based series of PCR-reactions that we determined are critical to prevent artefactual template switching and without which long-range epistatic interactions cannot be resolved.

**Results:** We use MrHAMER to precisely follow synonymous and non-synonymous changes in the HIV-1 Gag-Pol region (~5 kb) of individual viruses within a single host before treatment initiation and after failure of cART. We detect a hard selective sweep of a single pre-existing Gag-Pol variant containing

25 linked mutations from 0.1% enrichment prior to treatment initiation, to greater than 50% enrichment during antiviral therapy failure. These linked mutations are evenly spread throughout the Gag-Pol ORF, with 44% being synonymous, and 56% resulting in amino acid changes (including one canonical primary drug-resistance mutation that was previously undetected via clinical drug resistance testing). The enrichment of a high number of linked mutations (instead of more energetically favorable reversions) implies accumulated mutations play a compensatory role in viral fitness.

**Conclusion:** MrHAMER can identify long-range genetic correlates of intrahost viral evolution in response to antiviral therapy and immune pressure, and enable the identification of novel host-viral and viral-viral interfaces that play a role in viral pathogenesis and can be modulated for therapeutic benefit.



**Figure 1** – MrHAMER identifies genetically linked mutations in the HIV Gag-Pol region and reveals the clonal expansion of a pre-existing Gag-Pol genome harboring linked drug-resistant mutations in a patient undergoing virological failure. Visualized alignments of major Gag-Pol sequence clusters obtained in Treatment Naive (Naive) and Virological Failure (VF) samples. Reduction in viral sequence diversity is evident in VF samples.

**435 A MULTIPLEXED HIV DRUG RESISTANCE (DR) ASSAY TO SURVEY HIVDR MUTATIONS IN POL REGION**

**Joshua R. DeVos<sup>1</sup>**, Victor Sewe<sup>2</sup>, Grace Akinyi<sup>3</sup>, Kimberly D. McCarthy<sup>4</sup>, Muthoni Junghae<sup>4</sup>, Valarie Opolo<sup>3</sup>, Janin Nouhin<sup>5</sup>, Robert W. Shafer<sup>5</sup>, Artur Ramos<sup>1</sup>, Clement Zeh<sup>1</sup>, Heather Alexander<sup>1</sup>, Joy C. Chang<sup>1</sup>  
<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>Kenya Medical Research Institute-Centre for Global Health Research, Kisumu, Kenya, <sup>3</sup>Kenya Medical Research Institute, Kisumu, Kenya, <sup>4</sup>Centers for Disease Control and Prevention, Nairobi, Kenya, <sup>5</sup>Stanford University, Stanford, CA, USA

**Background:** As the WHO universal treatment policy using dolutegravir (DTG) for HIV treatment approaches full implementation globally, a user friendly, sensitive, low-cost HIVDR assay to survey Integrase (INT) HIVDR is urgently needed. By incorporating newly designed INT primers into Thermo Fisher (TF) HIV-1 Genotyping Assay, we constructed a multiplexed assay to detect HIVDR mutations of Protease, Reverse-transcriptase (PRRT), and INT in pol region, and evaluated assay performance.

**Methods:** The assay is designed to have a multiplexed reverse-transcription step to generate two amplicons (PRRT and INT) at the same time. Each amplicon is then further amplified and sequenced by Sanger sequencing individually for HIVDR detection. All sequences were analyzed by Stanford HIVdb program. A total of 190 clinical and analytical plasma and dried blood spots (DBS) samples from international HIVDR External Quality Assessment programs, INT clones, and commercial sources were used to evaluate subtype coverage, accuracy, assay sensitivity, precision, and reproducibility. RNA was extracted from 200 µL of plasma or one DBS spot by NucliSens (bioMérieux). RNA of 10 µL per sample was then processed using the assay. We assessed subtype coverage by evaluating 139 samples with previously known subtypes. We evaluated accuracy by testing 86 (INT) and 90 (PRRT) plasma and DBS samples that had reference sequences available. Assay sensitivity was evaluated by amplification success rate of samples with viral load (VL) from 1000 to 5,000, and >5000 copies/mL. Precision and reproducibility were evaluated by three plasma samples with different VL in five replicates respectively. All precision replicates were tested together. Reproducibility replicates were tested on different days by two people.

**Results:** All known subtype and CRF of group M were detected. For accuracy, 100% of INT samples (75 plasma, 11 DBS), 94.6% of PRRT plasma (57) and 100% of PRRT DBS (33) samples showed >98% homology with the reference sequences. All major PRRT and INT DR mutations were identified with good correlations. Plasma and DBS samples with low and high VL showed good amplification sensitivity (Table 1). The precision and reproducibility data showed > 98% sequence homology in each set of replicates.

**Conclusion:** This multiplexed HIVDR assay meets all WHO HIVDR assay performance criteria for surveillance, is sample saving, sensitive, and has

potential to preserve DTG and be a low-cost assay to monitor DR mutations in PRRT and INT regions.

**Table 1. Amplification Sensitivity**

| VL copies/mL | Sample Type | # of Samples | PRRT POS Rate (%) | INT POS Rate (%) | Sample Nature (clinical/analytical) |
|--------------|-------------|--------------|-------------------|------------------|-------------------------------------|
| >5000        | DBS         | 23           | 95.7 (22/23)      | 91.3 (21/23)     | 15/8                                |
|              | Plasma      | 78           | 97.4 (76/78)      | 97.4 (76/78)     | 34/44                               |
| 1000 to 5000 | DBS         | 25           | 88.0 (22/25)      | 88.0 (22/25)     | 4/21                                |
|              | Plasma      | 23           | 91.3 (21/23)      | 91.3 (21/23)     | 14/9                                |

**436 SIMULTANEOUS HIV QUANTIFICATION AND HIVDR DETECTION BY A SEMICONDUCTOR BIOCHIP SYSTEM**

**Kirsten A. Johnson<sup>1</sup>**, Janin Nouhin<sup>2</sup>, Ellen A. LaPrade<sup>1</sup>, Benjamin A. Pinsky<sup>2</sup>, Jessica A. Ebert<sup>1</sup>, Tran A. Van<sup>1</sup>, Arun A. Manickam<sup>1</sup>, Arjang A. Hassibi<sup>1</sup>, Robert W. Shafer<sup>2</sup>

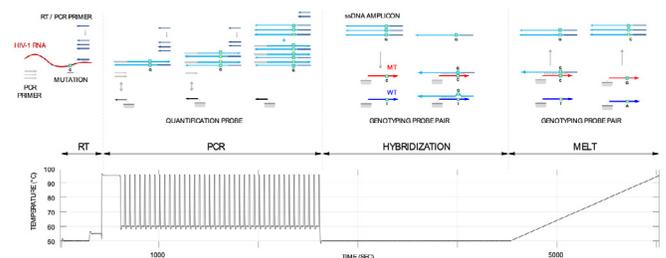
<sup>1</sup>InSilixa, Inc, Sunnyvale, CA, USA, <sup>2</sup>Stanford University, Stanford, CA, USA

**Background:** In regions that do not perform routine HIVDR testing, care providers are often uncertain how to manage PWH with VF because it is not possible to distinguish PWH who have HIVDR and require an ART change from those remaining infected with wildtype viruses.

**Methods:** We used a novel semiconductor biochip with a closed-tube near point-of-care NAAT to simultaneously measure VL and detect DRMs at 6 RT (65, 103, 106, 181, 184, 190) and 3 integrase (148, 155, 263) DRM positions. The biochip comprises a 32x32 oligonucleotide probe array immobilized on a biosensor that monitors parallel hybridization reactions during asymmetric multiplex PCR followed by melt curve analysis of the ssDNA PCR products (Figure 1). By thermocycling and measuring fluorescence without external heaters or imagers, the system obviates the need for complex equipment. VL is determined by probes that monitor depletion of the limiting PCR primers during a 6-plex PCR that amplifies the 5'UTR (for VL determination) plus 5 regions in RT and integrase (for VL determination and mutation detection). DRMs are detected by probes that differentially hybridize to DRM-containing PCR products.

**Results:** We performed 4 sets of experiments using a variety of DNA templates containing wildtype and mutant variants at each DRM position. The 1st set showed that probes complementary to the limiting primers yielded reproducible cycle thresholds (Ct) inversely proportional and linearly related to log DNA copy number. For 4 of 6 probes, the Ct difference between 50 copies and the no template control (NTC) sample was ≥2 cycles and between 100 copies and the NTC sample was ≥3 cycles suggesting that 50 and 100 copies could be unambiguously distinguished from the NTC. The 2nd set showed that melt-curve analysis reproducibly identified the correct codon at 9 DRM positions in mixtures of wildtype and mutant templates ranging from 20%-100%. The 3rd set showed that even at low template concentrations, asymmetric multiplex PCR generated sufficient ssDNA for melt-curve analysis for all probes with one exception. The 4th set showed that the use of additional probes with variant flanking sequences increased the proportion of samples that could be genotyped despite sample sequence variability.

**Conclusion:** Further development of this biochip system into a mass-deployable point-of-care test would streamline ART delivery and increase the likelihood that PWH would maintain virological suppression and be retained in care.



**Figure 1.** The 3-phase NAAT temperature profile and detection process: (1) RT-PCR (40 cycles); (2) Amplicon probe hybridization at 50°C; and (3) Amplicon-probe denaturation (melting) between 50°C and 95°C. The top half of the figure indicates the process occurring during each of the three NAAT phases. The bottom half of the figure shows the time in seconds on the X-axis and temperature on the Y-axis.

**437 DRUG RESISTANCE MUTATIONS IN HIV PROVIRUS ARE ASSOCIATED WITH HYPERMUTATIONS**

Yijia Li<sup>1</sup>, Behzad Etemad<sup>1</sup>, Ruth Dele-Oni<sup>2</sup>, Radwa Sharaf<sup>1</sup>, Ce Gao<sup>3</sup>, Xu Yu<sup>3</sup>, Jonathan Li<sup>1</sup>

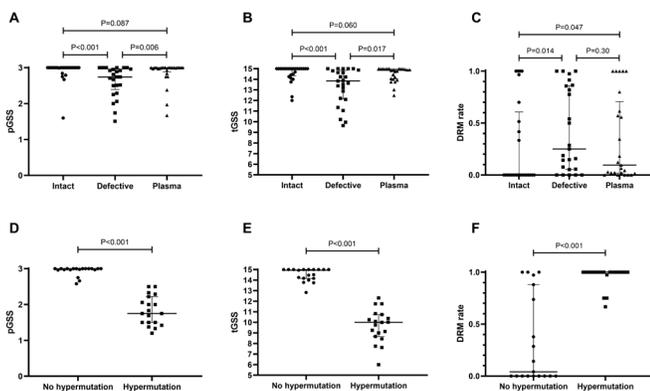
<sup>1</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>2</sup>Boston University, Boston, MA, USA, <sup>3</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

**Background:** HIV plasma virus drug resistance mutations (DRMs) tests are crucial to clinical care. However, current available methods require the plasma RNA copy number to be at least 500-1000 copies/ml and can only detect the major viral quasiespecies in peripheral blood. HIV proviral sequencing overcomes the limit of plasma viral load requirement by detecting all the "archival mutations", but its clinical relevance remains to be evaluated.

**Methods:** We included 25 participants from AIDS Clinical Trials Group (A371, A5068, A5197, A5170, and A5024) with available proviral and plasma viral sequences (either near full length or Pol sequences) and used the genotypic sensitivity score (GSS) to evaluate the level of resistance in their provirus and plasma virus. Defective sequences were further categorized as sequences with and without hypermutations. Personalized GSS score (pGSS, maximum value 3, indicating virus sensitive to current three ARTs) and total GSS score (tGSS, maximum value 15, indicating virus sensitive to a panel of 15 ARTs) were calculated using Stanford University HIV Drug Resistance Database to evaluate the level of resistance to a whole panel of ARTs and to certain ARTs that a participant was using. The rate of sequences with DRMs within each sequence compartment (intact, defective and plasma viral sequences) was calculated for each participant.

**Results:** Defective proviral sequences were less sensitive than intact proviral sequences or plasma sequences to a panel of 15 antiretroviral therapies (ART) and each participant's current ART, as reflected by significantly lower pGSS and tGSS (Figure A-B). They harbored more DRMs than other sequence compartments, with a median DRM rate of 0.25 compared to intact sequences (0.0, P=0.014) and plasma sequences (0.095, P=0.30) (Figure C). Hypermutated defective sequences were the major source of DRMs, with a median DRM rate of 1.0 compared to defective sequences without hypermutations (0.042, P<0.001, Figure D-F). Certain Apolipoprotein B Editing Complex 3 (APOBEC3)-related DRMs including reverse transcriptase gene mutations M184I, E138K, M230I, G190E and protease gene mutations M46I, D30N were enriched in hypermutated sequences but not in intact sequences or plasma sequences. The majority (>95%) of hypermutated sequences had premature stop codons due to APOBEC3.

**Conclusion:** Proviral sequencing may overestimate DRMs as a result of hypermutations. Removing hypermutated sequences is essential in the interpretation of proviral drug resistance testing.



**438 HIV-1 DNA GENOTYPING IS OFTEN VARIABLE IN REPEAT TESTING FROM SINGLE BLOOD DRAWS**

Michelle L. D'Antoni<sup>1</sup>, Kristen Andreatta<sup>1</sup>, Rima K. Acosta<sup>1</sup>, Hui Liu<sup>1</sup>, Yongwu Shao<sup>1</sup>, Kirsten L. White<sup>1</sup>

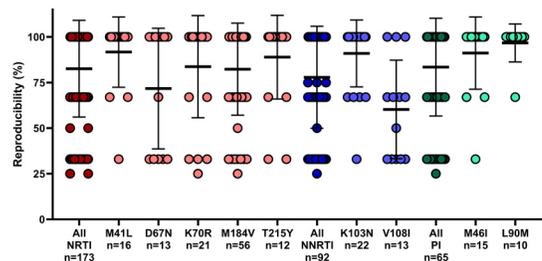
<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA

**Background:** HIV-1 DNA genotyping assesses archived drug resistance mutations (DRMs) in individuals with low plasma HIV RNA; however, assays detecting these mutations are insensitive. Here we seek to characterize the variability of DNA genotyping by quantifying the reproducibility of mutation reporting from multiple assays from a single blood draw.

**Methods:** DNA genotyping of protease (PR), reverse transcriptase (RT) and integrase (IN) used GenoSure Archive® (Monogram Biosciences, CA, USA) from whole blood from suppressed participants with documented resistance from 3 clinical trials (NCT03631732; NCT03110380; NCT03405935). Multiple tests (2-4) were run from each whole blood sample. Reproducibility of primary PR inhibitor (PI)-resistance (-R), nucleos(t)ide RT inhibitor (NRTI)-R, non-NRTI (NNRTI)-R, IN strand transfer inhibitor (INSTI)-R, and other/non-R mutations were calculated as the number (#) of times the mutation was detected/# of assays run (%). Means ± standard deviations (SD) were reported, and comparisons used Wilcoxon Rank Sum tests. A zero-truncated binomial model was used to estimate the probability of mutation detection.

**Results:** For 90 blood draws from 70 participants (79% male; age 56 y, 714 CD4 count, 86% subtype B), 257 genotype reports were analyzed. Overall, reproducibility was similar for all PR, RT and IN mutations (86±25%, 86±25% and 87±25%, respectively). A total of 15 PI, 18 NRTI and 19 NNRTI primary DRMs were detected in 21, 43, and 31 participants, respectively, with reproducibility of 84±27%, 83±26%, 78±28% (Fig). INSTI-R occurrence was too low (n=2) for further analyses. The NRTI DRM M184V had a reproducibility of 82±25%, with 14% of cases being detected in 1/4 or 1/3 reports, 23% in 1/2, 2/4, or 2/3 reports, and 63% being detected in all reports. Reproducibility did not differ among drug classes. Reproducibility of polymorphisms and other non-R RT mutations was significantly higher than for primary NRTI and NNRTI DRMs (p<0.05). Reproducibility of primary DRMs was 10-16% higher when detected by historical genotype compared to not being reported or not having data (p<0.05). By modelling, if a person had a PI, NRTI, or NNRTI DRM, the probability of it being reported by the assay was 76-80%.

**Conclusion:** Mean reproducibility of ~80% with standard deviations of ~25% indicate that detection of mutations is variable. DNA genotyping may aid clinicians when switching HIV regimens, but these data reinforce the need to interpret tests with caution, as not all mutations may be reported.



**439 REINFECTION WITH THE HEPATITIS C VIRUS IN MEN WHO HAVE SEX WITH MEN**

Christoph Boesecke<sup>1</sup>, Knud C. Schewe<sup>2</sup>, Thomas Lutz<sup>3</sup>, Stefan Mauss<sup>4</sup>, Stefan Christensen<sup>5</sup>, Sonia Jain<sup>6</sup>, Feng He<sup>6</sup>, Michael Sabranski<sup>2</sup>, Stephan Grunwald<sup>7</sup>, Markus Bickel<sup>3</sup>, Natasha K. Martin<sup>6</sup>, Jürgen K. Rockstroh<sup>1</sup>, Patrick Ingiliz<sup>7</sup>

<sup>1</sup>Bonn University Hospital, Bonn, Germany, <sup>2</sup>Infektologisches Centrum, Hamburg, Germany, <sup>3</sup>Infektologikum, Frankfurt, Germany, <sup>4</sup>Center for HIV and Hepatogastroenterology, Düsseldorf, Germany, <sup>5</sup>Muenster University Hospital, Muenster, Germany, <sup>6</sup>University of California San Diego, La Jolla, CA, USA, <sup>7</sup>Center for Infectiology, Berlin, Germany

**Background:** Reinfection with the hepatitis C virus (HCV) after cure has been identified as a major challenge for HCV micro-elimination targets in high-risk groups. In men who have sex with men (MSM), even multiple HCV reinfections have been described, and a specific risk behavior pattern may have a significant impact on management and prevention. Here, we assess factors associated with HCV reinfection(s) among MSM in Germany.

**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 for HIV- MSM and HIV pre-exposure prophylaxis (PrEP) sites. Virologic data, HCV treatment data, risk factors, and behavior as well as liver disease assessment are assessed regularly. In this analysis, patients who were diagnosed with recently acquired HCV reinfection since 2014 were evaluated as a subgroup and compared to patients with a single HCV infection.

**Results:** Between January 2014 and September 2020, 81/214 (37.8%) men with recently acquired HCV reinfection were included, and during a follow-up time of 416 person-years (py) the incidence rate for HCV reinfection was 18.5/100 py

(95% confidence interval (CI) 14.6 – 23.1). 75 subjects had complete datasets : HCV reinfection occurred after treatment-induced cure in 60 (80%) and after spontaneous clearance in 13 (17.3%) cases. Only two reinfections occurred in HIV-negative individuals. Most reinfections were detected through routine HCV RNA testing (68%), followed by testing for ALT elevation (25.6%). Compared to patients with primary HCV infection, reinfection cases were older (OR 1.06, p<0.001), more often coinfecting with HIV (OR 5.02, p=0.035), and declared more often the use of crystal methamphetamine (OR 5.9, p=0.041) and we identified a trend towards declared ketamine use (OR 6.0, p=0.07). Compared to patients with a single reinfection (n=58) patients with multiple reinfections (n=23) were not significantly different with regards to demographics, STD history, mode of transmission, or substance use.

**Conclusion:** In the German NoCo cohort, HCV reinfection is frequent, especially in an aging HIV coinfecting population with methamphetamine use. The role of recreational ketamine in this setting needs further study, as well as the (so far) infrequent detection of HCV reinfection in the HIV-negative MSM population. No specific pattern could be identified for patients with multiple HCV reinfections.

**440 COST-EFFECTIVENESS OF HCV TESTING STRATEGIES FOR HCV ELIMINATION AMONG MSM IN THE US**



**Antoine Chaillon**<sup>1</sup>, Louis MacGregor<sup>2</sup>, Peter Vickerman<sup>2</sup>, Daniel Fierer<sup>3</sup>, Natasha Martin<sup>1</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>University of Bristol, Bristol, UK, <sup>3</sup>Mt Sinai School of Medicine, New York, NY, USA

**Background:** Background: Despite current hepatitis C virus (HCV) elimination efforts in the United States (US), men who have sex with men (MSM), both with HIV and without HIV, continue to have high rates of HCV transmission. We hypothesized that better testing could result in a lower rate of transmission. We therefore used a cost-effectiveness model to determine the optimal HCV testing strategies for HCV elimination among MSM.

**Methods:** Methods: We adapted a cost-effectiveness model of HIV and HCV transmission among MSM to determine the cost-effectiveness of improving HCV testing strategies among MSM in the US. The model assumed 15% HIV prevalence among MSM, 8% HCV prevalence among MSM with HIV, and 25% PrEP coverage among MSM without HIV. We evaluated testing strategies that could achieve a 90% reduction in HCV incidence from 2015 as a baseline, through 2030. At baseline, we assumed no systematic HCV screening (i.e. testing only for symptoms) in MSM without HIV not using PrEP (PrEP non-users) and the currently recommended frequency of HCV screening among MSM with HIV (~50%/year). We assessed the following HCV case-finding strategies: screening in parallel with HIV testing in PrEP non-users; screening every 12/6/3 months in MSM using PrEP; and screening every 6 months in MSM with HIV. These strategies were considered alone and in combination, with the cost-effectiveness compared incrementally. Costs (USD) and quality adjusted life-years (QALYs) were assessed to estimate the mean incremental cost-effectiveness ratio (ICER) through 2050, compared to a willingness-to-pay (WTP) threshold of \$100,000/QALY gained.

**Results:** Results: Our economic model predicted the optimal HCV testing strategy to achieve HCV elimination among MSM in the US to be every 6 months for MSM with HIV; annually for MSM using PrEP; and at the time of HIV testing for PrEP non-users. This testing schedule resulted in an incremental ICER of \$35,000/QALY gained (Table 1).

**Conclusion:** Conclusions: HCV elimination can be achieved among MSM in U.S. by a relatively nominal and logistically feasible increase in the frequency of HCV screening over what is currently recommended, and is cost-effective.

Table 1. Cost-effectiveness of HCV testing strategies among MSM. An incremental analysis is performed, excluding dominated or weakly dominated strategies.

| Optimal order of implementation of HCV testing strategies in U.S. MSM.            | Baseline | HIV-negative non-PrEP users screened when HIV-tested; | PrEP users screened yearly; HIV-negative non-PrEP users screened when HIV-tested; | PrEP users screened yearly; HIV-negative non-PrEP users screened when HIV-diagnosed screened 6 monthly | PrEP users screened 6-monthly; HIV-negative non-PrEP users screened when HIV-tested; HIV-diagnosed screened 6 monthly | PrEP users screened 3-monthly; HIV-negative non-PrEP users screened when HIV-tested; HIV-diagnosed screened 6 monthly |
|---|----------|---|---|--|---|---|
| Is 90% reduction in incidence target reached by 2030 among MSM?                   | No       | Yes   | Yes   | Yes  | Yes   | Yes   |
| QALYs gained compared to next least costly scenario                               | -        | 69,413  | 9,977   | 4,141  | 2,645   | 2,099   |
| Incremental costs compared to next least costly scenario (in hundred millions \$) | -        | 544   | 332   | 146  | 399   | 824   |
| Mean ICER (\$ per QALY gained) compared to next least costly scenario             | -        | 7,837   | 33,270  | 35,162   | 150,800   | 392,415   |

**441 HIV/HCV COINFECTION TRENDS IN SPAIN (2015-2019)**

**Chiara Fanciulli**<sup>1</sup>, Juan Berenguer<sup>1</sup>, Carmen Busca Arenzana<sup>2</sup>, María Jesús Vivancos<sup>3</sup>, María Jesús Tellez<sup>4</sup>, Lourdes Domínguez<sup>5</sup>, Pere Domingo<sup>6</sup>, Jordi Navarro<sup>7</sup>, Jesús Santos<sup>8</sup>, José A. Iribarren<sup>9</sup>, Luis Morano<sup>10</sup>, Marta De Miguel<sup>11</sup>, Inmaculada Jarrín<sup>12</sup>, Juan González-García<sup>13</sup>, for the GeSIDA 8514 Study Group <sup>1</sup>Hospital General Universitario Gregorio Marañón, Madrid, Spain, <sup>2</sup>Hospital La Paz Institute for Health Research, Madrid, Spain, <sup>3</sup>Hospital Ramón y Cajal, Madrid, Spain, <sup>4</sup>Hospital Clínico San Carlos, Madrid, Spain, <sup>5</sup>Hospital Universitario 12 de Octubre, Madrid, Spain, <sup>6</sup>Hospital Sant Pau, Barcelona, Spain, <sup>7</sup>Hospital Universitario de la Vall d'Hebron, Barcelona, Spain, <sup>8</sup>Hospital Universitario Virgen de la Victoria, Malaga, Spain, <sup>9</sup>Hospital Donostia, San Sebastián, Spain, <sup>10</sup>Hospital Universitario Alvaro Cunqueiro, Vigo, Spain, <sup>11</sup>Fundación SEIMC-GeSIDA, Madrid, Spain, <sup>12</sup>Instituto de Salud Carlos III, Madrid, Spain, <sup>13</sup>La Paz University Hospital, Madrid, Spain

**Background:** We assessed the prevalence of anti-HCV antibodies (HCV-Ab) and active HCV infection (HCV-RNA-positive) in people living with HIV (PLWH) in Spain in 2019 and compared the results with four similar studies performed yearly from 2015 to 2018.

**Methods:** The study was performed in 41 centers (October-November, 2019). The sample size was estimated for an accuracy of 1.0%, the number of patients from each hospital was determined by proportional allocation, and patients were selected using simple random sampling. All oral DAA-based therapy has been available in Spain since the third trimester of 2014. Since June 2017, free access to treatment has been available to all HCV-infected individuals.

**Results:** The reference population comprised 41,973 PLWH, and the sample size was 1,325. HCV serostatus was known in 1,316 (99.3%), and 376 (28.6%) were HCV Ab-positive (78.7% PWID and 7.7% MSM). Of the 376 HCV Ab-positive patients, 291 cleared HCV after anti-HCV therapy, 55 cleared HCV spontaneously, 29 were HCV-RNA-positive, and 1 had unknown HCV-RNA. The prevalence of HCV-RNA-positive was, therefore, 2.2%. As 11 of 29 patients were receiving DAAs, and assuming treatment effectiveness of 95%, the HCV-RNA-positive prevalence could be considered to be 1.4%. Reasons for not receiving anti-HCV therapy in 18 patients included physician decision (N=5), loss to follow-up (N=3), patient refusal (N=2), and unknown reasons (N=4). Of the 29 HCV-RNA-positive patients, the infection was chronic in 24, acute/recent in 1, and unknown duration in 4. HCV-related liver cirrhosis was present in 71 (5.4%) PLWH overall, 3 (10.3%) HCV-RNA-positives, and 68 (23.4%) of those who cleared HCV after anti-HCV therapy (P=.04). The prevalence of HCV Ab decreased steadily from 37.7% in 2015 to 28.6% in 2019 (P <.001). Likewise, HCV-RNA prevalence decreased from 22.1% in 2015 to 2.2% in 2019 (P <.001). Anti-HCV treatment uptake increased from 53.9% in 2015 to 95.0% in 2019 (P <.001) (Table).

**Conclusion:** Active HCV infection among PLWH in Spain at the end of 2019 was 2.2%, that is, 90.0% lower than in 2015, meaning that elimination of HCV infection among PLWH in Spain is an achievable goal shortly. Increased exposure to DAAs was likely the main reason for this sharp decrease. Despite the high coverage and effectiveness of DAA-based treatment, HCV-related cirrhosis among those successfully treated for HCV remains significant in this population.

Table. Trends in HIV/HCV coinfection in Spain, 2015-2019

|                           | 2015   | 2016   | 2017   | 2018   | 2019   | P trend |
|---------------------------|--------|--------|--------|--------|--------|---------|
| Centers                   | 41     | 43     | 43     | 43     | 41     |         |
| Reference population      | 35,791 | 38,904 | 40,322 | 40,650 | 41,973 |         |
| Sample size               | 1,867  | 1,588  | 1,690  | 1,733  | 1,325  |         |
| Tested for HCV Ab         | 98.7%  | 99.8%  | 99.1%  | 99.3%  | 99.3%  |         |
| HCV Ab-positive           | 37.7%  | 34.6%  | 34.0%  | 33.6%  | 28.6%  | <.001   |
| HCV-RNA-positive          | 22.1%  | 11.8%  | 8.0%   | 3.7%   | 2.2%   | <.001   |
| Anti-HCV treatment uptake | 59.3%  | 74.7%  | 82.4%  | 92.2%  | 95.0%  | <.001   |

**442 NO CHANGE IN INCIDENCE OF RECENTLY ACQUIRED HCV IN HIV+ MSM IN GERMANY (NOCO COHORT)**

**Patrick Ingiliz<sup>1</sup>**, Natasha Martin<sup>2</sup>, Thomas Lutz<sup>3</sup>, Knud C. Schewe<sup>4</sup>, Stefan Mauss<sup>5</sup>, Stefan Christensen<sup>6</sup>, Sonia Jain<sup>7</sup>, Feng He<sup>1</sup>, Martin Daeumer<sup>8</sup>, Axel J. Schmidt<sup>9</sup>, Michael Sabranski<sup>6</sup>, Axel Baumgarten<sup>1</sup>, Markus Bickel<sup>3</sup>, Jürgen K. Rockstroh<sup>10</sup>, Christoph Boesecke<sup>10</sup>

<sup>1</sup>Center for Infectiology, Berlin, Germany, <sup>2</sup>Division of Infectious Diseases and Global Public Health, University of California San Diego, San Diego, CA, USA, <sup>3</sup>Infectiologikum, Frankfurt, Germany, <sup>4</sup>Infectiologisches Centrum, Hamburg, Germany, <sup>5</sup>Center for HIV and Hepatogastroenterology, Düsseldorf, Germany, <sup>6</sup>Muenster University Hospital, Muenster, Germany, <sup>7</sup>University of California San Diego, La Jolla, CA, USA, <sup>8</sup>Institute for Genetics and Immunology, Kaiserslautern, Germany, <sup>9</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>10</sup>Bonn University Hospital, Bonn, Germany

**Background:** Directly-acting antiviral agents (DAA) against the hepatitis C virus (HCV) have been available in Germany since February 2014. 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.

**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. 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 September 2020, 214 MSM with recently acquired HCV infection were included. A majority were Caucasian (94%), and mean age was 45.5 years (standard deviation, SD, 9.64). At HCV diagnosis, median ALT level was 201 U/L (interquartile range, IQR, 86–509), and median HCV viral load was 483,028 IU/mL (IQR 77,804 – 2,525,000). The most prevalent HCV genotype was 1a (58.9%), followed by genotype 4d (16.4%), and 3a (6.1%). The risk factors for HCV acquisition were as follows: MSM: 92.5%, intravenous drug use: 2.8%, intranasal drug use: 0.9%, other: 0.5%. A subgroup of 17 (7.8%) MSM were not co-infected with HIV, of whom 10 (58.8%) were using PrEP. In 198/214 (92.5%) patients outcome data were available: DAA treatment was documented in 148 patients (74.7%), 16/198 (8.1%) had a spontaneous clearance, and in 34 patients (17.2%) treatment was not started, in most cases (35.3%) due to health insurance constraints. Among those treated, DAAs were initiated a median 6.6 months (IQR 3.4 to 9.6) after diagnosis; all treated patients achieved a sustained virologic response (SVR), or treatment was still ongoing (14%). Between 2014-2019, 26-36 patients were diagnosed with recently acquired HCV annually. In relation to all HIV-positive MSM under care, the incidence was 0.32 – 0.39% per year with no significant change over time.

**Conclusion:** In this preliminary analysis from the German NoCo cohort, HCV incidence remained stable despite a broad use of DAAs. Delays to HCV treatment initiation and health insurance constraints may fuel ongoing HCV transmission, as well as continuous or even increasing risk behavior.

**443 HEPATITIS C CASCADE OF CARE IN HIV/HCV-COINFECTED PERSONS IN EUROPE IN THE DAA ERA**

**Olga Fursa<sup>1</sup>**, Amanda Mcroft<sup>2</sup>, Jeffrey V. Lazarus<sup>3</sup>, Sarah Amele<sup>2</sup>, Jens D. Lundgren<sup>1</sup>, Raimonda Matulionyte<sup>4</sup>, Line D. Rasmussen<sup>5</sup>, Jürgen K. Rockstroh<sup>6</sup>, Milosz Parczewski<sup>7</sup>, David Jilich<sup>8</sup>, Santiago Moreno<sup>9</sup>, Anna Vassilenko<sup>10</sup>, Karine Lacombe<sup>11</sup>, Lars Peters<sup>1</sup>, for the EuroSIDA Study Group

<sup>1</sup>Centre of Excellence for Health, Immunity and Infections, Copenhagen, Denmark, <sup>2</sup>Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, University College London, London, UK, <sup>3</sup>Barcelona Institute for Global Health, Barcelona, Spain, <sup>4</sup>Vilnius University, Vilnius, Lithuania, <sup>5</sup>Odense University Hospital, Odense, Denmark, <sup>6</sup>Bonn University Hospital, Bonn, Germany, <sup>7</sup>Pomeranian Medical University, Szczecin, Poland, <sup>8</sup>Charles University in Prague and Na Bulovce Hospital, Prague, Czech Republic, <sup>9</sup>Hospital Universitario Ramón y Cajal, Madrid, Spain, <sup>10</sup>Belarusian State Medical University, Minsk, Belarus, <sup>11</sup>Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France

**Background:** The WHO global hepatitis C (HCV) elimination targets include diagnosing 90% and treating 80% of HCV infected individuals by 2030. We described the HCV cascade of care (CoC) for people living with HIV (PLHIV) across Europe to assess progress towards reaching these two targets.

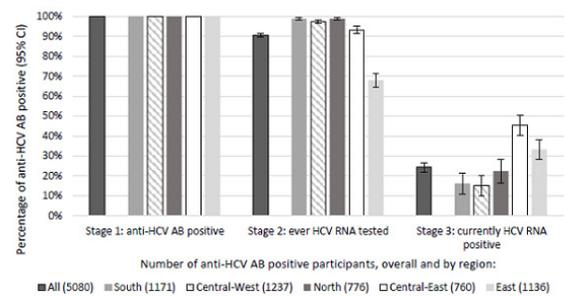
**Methods:** HIV/HCV-coinfected participants in the EuroSIDA cohort under prospective follow-up at 1 October 2018 were described using a CoC with 3

diagnostic stages - anti-HCV positive, ever HCV RNA tested, currently HCV RNA positive; and 7 treatment stages - ever chronically infected (multiple imputation for persons with missing HCV RNA test data), ever diagnosed with chronic HCV, ever treated, completed treatment, sufficient follow-up available, follow-up HCV RNA available, cured. CoC were compared across five European regions and 20 countries enrolling >50 persons.

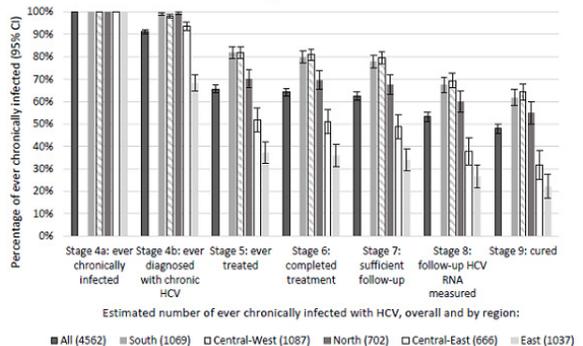
**Results:** Of 5,080 anti-HCV positive persons, 4,609 (90.7%, 95% confidence interval (CI) 89.9-91.6) were ever HCV RNA tested (Figure 1A) and 24.3% of individuals (95% CI 21.9-26.7) were currently HCV RNA positive, with higher prevalence in Central-East and East (45.4% and 33.2%, respectively). Among all participating countries the proportion of currently HCV RNA positive was the highest in Estonia (62% of 160 anti-HCV positive) and lowest in Austria (4.8% of 124). An estimated 4,562 (89.8%, 95% CI 88.9-90.7) anti-HCV positive individuals have been ever chronically infected, of which 4,155 persons (90.1%, 95% CI 89.2-91.0) have been ever diagnosed with chronic HCV (Figure 1B). In Eastern Europe, 68.4% of chronic infections have ever been diagnosed, with >93% in the other four regions. Overall, 2,989 persons have ever been treated (65.5% of the ever chronically infected, 95% CI 63.8-67.2) and 2,186 individuals (47.9% of the ever chronically infected, 95% CI 45.8-50) were cured. Cure proportion ranged from 6.7% of 356 ever chronically infected in Belarus to 87.2% of 109 in Austria.

**Conclusion:** In all regions except Eastern Europe, >90% of anti-HCV positive PLHIV under follow-up at 1 October 2018 have been tested for HCV RNA. In South and Central-West, >80% ever chronically HCV infected PLHIV have ever received treatment. Overall, the proportion with cured HCV infection did not exceed 80% in any region with significant heterogeneity between countries. Increased access to affordable direct acting antivirals, particularly in Eastern Europe, is required to achieve HCV elimination by 2030 among PLHIV in Europe.

**Figure 1A**



**Figure 1B**



**444 ADEQUATE DACLATASVIR EXPOSURES IN CHILDREN 14-35 KG WITH AVAILABLE ADULT FORMULATIONS**

**Tim R. Cressey<sup>1</sup>**, Maggie Abbassi<sup>2</sup>, Marc Lallemand<sup>3</sup>, Giuseppe Indolfi<sup>4</sup>, Moge Al-Nahari<sup>2</sup>, Samar Farid<sup>2</sup>, Philippa Easterbrook<sup>5</sup>, Martina Penazzato<sup>5</sup>, Manal H. El-Sayed<sup>6</sup>

<sup>1</sup>Chiang Mai University, Chiang Mai, Thailand, <sup>2</sup>Cairo University, Cairo, Egypt, <sup>3</sup>PENTA Foundation, Padova, Italy, <sup>4</sup>University of Florence, Florence, Italy, <sup>5</sup>World Health Organization, Geneva, Switzerland, <sup>6</sup>Ain Shams University, Cairo, Egypt

**Background:** World Health Organization 2018 guidelines recommend Sofosbuvir (SOF)/Daclatasvir (DCV) as a pangenotypic regimen for the treatment of adults with chronic HCV infection. SOF/DAC is widely available as low-cost generic formulation in low and middle-income countries (LMICs). Recent studies

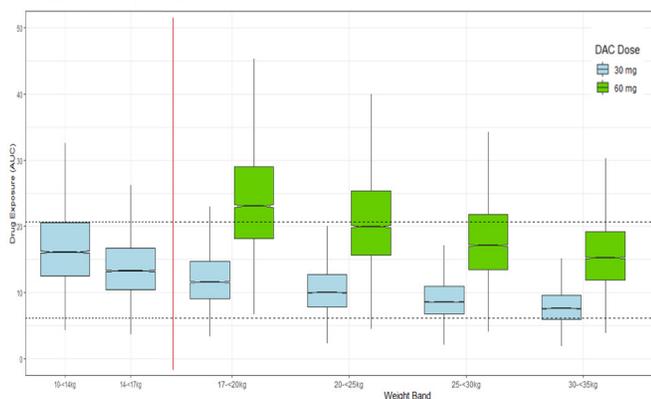
in adolescents ( $\geq 12$  to  $< 18$ ) using SOF/DCV 400/60 mg once-daily (OD) adult dose reported excellent efficacy and safety. DCV pharmacokinetic (PK) data in younger children are lacking. Within the framework of the Global Accelerator for Pediatric Formulations (GAPf), we performed a population PK analysis using data from adolescents to predict DCV exposure in children  $< 35$  kg to determine the lowest body weight children could be treated with the available DCV formulations (60 and 30 mg).

**Methods:** Data from HCV-infected adolescents receiving SOF/DCV (400/60 mg, OD) who participated in a PK study in Egypt were used for PK model development. Intensive PK sampling was performed pre-dose, then 0.5, 1.0, 1.5, 2, 4, 8, 12, and 24 hrs post-dose. PK parameters were estimated using a population approach (NONMEM VII). Monte Carlo simulations were run for virtual children between 10 to  $< 35$  kg receiving 60 mg or 30 mg OD and DCV exposures (AUC<sub>0-24</sub>) were compared with the expected adults range (6.15 to 20.63  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ).

**Results:** Seventeen HCV-infected adolescents (13 males) provided 151 DCV concentrations. Median (range) age was 14 (11-18) years and weight 50 (32-63) kg. DCV plasma concentrations were best described by a 1-compartment model with transit absorption compartments. Body weight (allometrically scaled) and albumin influenced DCV PK parameters. DCV oral clearance and volume of distribution were 7.05 L/hr/70kg and 95.8 L/70kg. In adolescents using 60 mg DCV OD, mean (SD) DCV AUC<sub>0-24</sub>, C<sub>max</sub> and C<sub>last</sub> were 12,004 (4,916) ng $\cdot$ hr/mL, 1,182 (393) ng/mL and 194 (168) ng/mL, respectively; while predicted to be 9,808 (3,949) ng $\cdot$ hr/mL, 1,039 (316) ng/mL and 148 (129) ng/mL in children 17 to  $< 35$  kg receiving 30 mg OD. Simulations showed that the proportion of children with DCV exposures above expected range rapidly increased for children  $< 30$  kg using 60 mg OD; and similarly for children 10-14 kg using 30 mg (Fig 1).

**Conclusion:** DCV 30 mg OD is expected to provide exposures comparable to adult values in children 14-35 kg. Our results suggest that children could be treated using currently available low-cost DCV formulations together with approved doses of pediatric SOF formulations, thus expanding access to HCV treatment.

**Figure 1:** Predicted daclatasvir exposure (AUC<sub>0-24</sub>) in children receiving DAC 30 vs 60 mg OD over the weight range 10 to  $< 35$  kg



#### 445 FAILURE TO ACHIEVE HCV MICROELIMINATION AMONG PLWH IN SPAIN

**Alejandro Gonzalez-Serna**<sup>1</sup>, Juan Macias<sup>1</sup>, Rosario Palacios<sup>2</sup>, Cristina Gómez-Ayerbe<sup>2</sup>, Francisco Tellez<sup>3</sup>, Antonio Rivero-Juarez<sup>4</sup>, Marta Fernandez-Fuertes<sup>1</sup>, Jesús Santos<sup>2</sup>, Luis M Real<sup>1</sup>, Gonzalez-Domenech Carmen María<sup>2</sup>, Jesus Gomez-Mateos<sup>1</sup>, Juan A. Pineda<sup>1</sup>

<sup>1</sup>Hospital Universitario de Valme, Seville, Spain, <sup>2</sup>Hospital Virgen de la Victoria, Málaga, Spain, <sup>3</sup>Hospital de Puerto Real, Puerto Real, Spain, <sup>4</sup>Hospital Universitario Reina Sofia, Cordoba, Spain

**Background:** Spain is close to HCV microelimination, so rates of recently acquired HCV infection (RAHC) should decrease. Nowadays, men who have sex with men (MSM) carry the highest risk of HCV acquisition. Our aim was to estimate the incidence of and the factors associated with RAHC, together with reinfection rates, among patients infected with HIV through sexual intercourse.

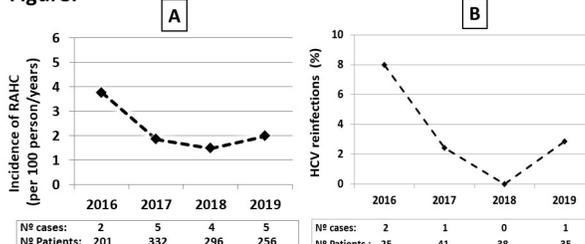
**Methods:** This was a prospective cohort study conducted at four hospitals in Spain. MSM and non-MSM infected with HIV through sexual intercourse patients consecutively attending these hospitals were included. Primary RAHC infection was diagnosed when anti-HCV antibody seroconversion was

documented. In anti-HCV positive patients, initially without HCV viremia, a diagnosis of reinfection was established if plasma HCV RNA was detected.

**Results:** Three hundred and fifty patients tested negative for anti-HCV at baseline and had at least one follow-up visit. Among them, there were 16 RAHC cases from 2016 to 2019. RAHC incidence rates [IR (95% CI)] per 100 person-years (py) were 3.77 (0.5-12.9) in 2016, 1.85 (0.6-4.3) in 2017, 1.49 (0.4-3.8) in 2018 and 1.98 (0.6-4.5) in 2019 (Figure 1A). Only previous sexually transmitted infections (IRR: 18.23; 95% CI 1.93-172.1;  $p=0.011$ ), male sex (IRR: 8.33; 95% CI 1.38-54.15;  $p=0.026$ ) and sharing chem-sex drugs (IRR: 4.93; 95% CI 1.17-20.76;  $p=0.030$ ), were independently associated with RAHC. Four of 42 (9.5%) patients became reinfected (Figure 1B).

**Conclusion:** The incidence of RAHC among HIV-infected patients showed a decrease after 2016, although a lower but steady incidence of residual cases still remains. HCV reinfections showed a similar pattern. New infections were associated with sharing chem-sex drugs among MSM. This suggests that the elimination of HCV infection in patients infected with HIV through sexual intercourse slowed down since 2017, likely due to sexual contacts with HCV-infected MSM without HIV-infection who remain undiagnosed.

**Figure:**



#### 446 SELF-TESTING FOR HCV: MULTICOUNTRY EVIDENCE ON USABILITY AND ACCEPTABILITY

**Elena Ivanova Reipold**<sup>1</sup>, Thi Thuy Van Nguyen<sup>2</sup>, Gamal Shiha<sup>3</sup>, Ketevan Stvilia<sup>4</sup>, Aliza Monroe-Wise<sup>5</sup>, Cheng Wang<sup>6</sup>, Muhammad Jamil<sup>7</sup>, Cheryl C. Johnson<sup>7</sup>, Philippa Easterbrook<sup>7</sup>

<sup>1</sup>Foundation for Innovative New Diagnostics, Geneva, Switzerland, <sup>2</sup>World Health Organization, Vietnam Country Office, Hanoi, Viet Nam, <sup>3</sup>Mansoura University, Mansoura, Egypt, <sup>4</sup>National Center for Disease Control, Tbilisi, Georgia, <sup>5</sup>University of Washington, Seattle, WA, USA, <sup>6</sup>Guangxi Medical University, Nanning, China, <sup>7</sup>World Health Organization, Geneva, Switzerland

**Background:** Globally,  $\leq 20\%$  of all persons with hepatitis C (HCV) infection have been tested and only one quarter of diagnosed persons have been treated. Self-testing for HCV antibodies (HCVST) may be an additional strategy to expand access to HCV testing and support elimination efforts. We undertook studies to assess usability and acceptability of HCVST in general population as well as key populations: men who have sex with men (MSM) and people who inject drugs (PWID).

**Methods:** Observational studies were conducted in five countries: Egypt (general population); China (MSM); Kenya (PWID); Vietnam and Georgia (PWID and MSM). Oral fluid OraQuick® HCV Rapid Antibody Test with Instructions for Use (IFU) adapted for ST was used as a prototype HCVST kit. Participants were provided written and pictorial IFU and then conducted ST in a private room with a trained observer. In Egypt, in addition to IFU, study personnel provided a one-to-one demonstration on how to use the test. Usability was evaluated through observer assessment of errors and difficulties during ST using a standardized checklist; and acceptability using a semi-structured questionnaire. HCVST results were read and interpreted by participants and then re-read by the observer. All participants were re-tested with a professional use OraQuick® HCV Test performed by a trained provider.

**Results:** A total of 775 participants were enrolled across five studies. Participants completing all testing steps without any mistakes was greatest in Egypt and Georgia ( $>70\%$ ), and lowest in PWID from Kenya (30%) and Vietnam (46%). The most common error was incorrect sample collection. Inter-reader agreement ranged from 86% to 99%, and inter-operator agreement from 85% to 99%. The majority of PWID from Vietnam and Kenya required assistance in performing HCVST. The proportion of participants who found the kit very easy or easy to conduct ranged from 55% in Egypt and 66% in Kenya, to more than 80% in other countries. Acceptability was high with  $> 90\%$  of participants in four

countries willing to use HCVST again and who would recommend it to family and friends.

**Conclusion:** These are the first studies globally to demonstrate high usability and acceptability of HCVST in both general and key populations. While most users self-tested with ease, assisted self-testing models are needed for some populations such as PWID. HCVST is an important strategy for further consideration as it may be a promising tool for increasing coverage and achieving elimination goals.

|  | Egypt            |              | China         |              | Vietnam      |              | Georgia       |  | Kenya |  |
|--|------------------|--------------|---------------|--------------|--------------|--------------|---------------|--|-------|--|
|  | Gen Pop<br>n=116 | MSM<br>n=100 | PWID<br>n=105 | MSM<br>n=104 | PWID<br>n=90 | MSM<br>n=100 | PWID<br>n=150 |  |       |  |
| <b>OBSERVED SELF-TESTING</b>                               |                  |              |               |              |              |              |               |  |       |  |
| Completed all testing steps correctly without errors       | 102 (88%)        | 55 (55%)     | 48 (46%)      | 70 (67%)     | 64 (71%)     | 84 (84%)     | 44 (30%)      |  |       |  |
| Completed all testing steps correctly without difficulties | 54 (47%)         | 43 (43%)     | 30 (29%)      | 56 (54%)     | 61 (68%)     | 82 (82%)     | 26 (17%)      |  |       |  |
| Assistance provided  | 14 (12%)         | 4 (4%)       | 70 (67%)      | 18 (17%)     | 20 (22%)     | 8 (8%)       | 115 (77%)     |  |       |  |
| Inter-reader agreement                                     | 86%              | 97%          | 88%           | 99%          | 97%          | 99%          | 97%           |  |       |  |
| Inter-operator agreement                                   | 93%              | 98%          | 85%           | 100%         | 94%          | 99%          | 97%           |  |       |  |
| <b>PARTICIPANT FEEDBACK</b>                                | n=116            | n=100        | n=105         | n=104        | n=90         | n=100        | n=150         |  |       |  |
| Found self-testing procedure easy/very easy                | 55 (46%)         | 94 (94%)     | 100 (96%)     | 98 (94%)     | 80 (80%)     | 89 (89%)     | 99 (66%)      |  |       |  |
| Consider HCVST accurate                                    | 64 (57%)         | 54 (54%)     | 102 (97%)     | 101 (97%)    | 81 (81%)     | 80 (80%)     | 141 (94%)     |  |       |  |
| Would use the self-test again                              | 112 (97%)        | 76 (76%)     | 96 (91%)      | 102 (98%)    | 91 (91%)     | 99 (99%)     | 143 (95%)     |  |       |  |
| Would take the self-test to family/friends                 | 109 (94%)        | 74 (74%)     | 104 (99%)     | 101 (97%)    | 95 (95%)     | 94 (94%)     | 144 (96%)     |  |       |  |

**447 DRUG-USE STIGMA AND HEPATITIS C VIRUS INFECTION AMONG PWID IN INDIA**

**Eshan U. Patel<sup>1</sup>**, Sunil S. Solomon<sup>1</sup>, Gregory M. Lucas<sup>1</sup>, Allison M. McFall<sup>1</sup>, Aylur K. Srikrishnan<sup>2</sup>, Muniratnam S. Kumar<sup>2</sup>, Oliver Laeyendecker<sup>3</sup>, David C. Celentano<sup>1</sup>, David L. Thomas<sup>1</sup>, Thomas Quinn<sup>3</sup>, Shruti H. Mehta<sup>1</sup>

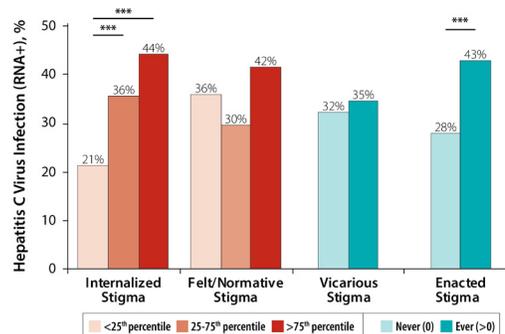
<sup>1</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>YR Gaitonde Center for AIDS Research and Education, Chennai, India, <sup>3</sup>National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA

**Background:** Although drug use stigma is globally pervasive, empirical evidence of its role in hepatitis C virus (HCV) transmission is limited. We measured the association between drug use stigma and active HCV infection among community-based people who inject drugs (PWID) in India.

**Methods:** Between 8/2016 and 5/2017, a cross-sectional sample of PWID was recruited from 12 Indian cities (~1000/city) using respondent-driven sampling. Participants were ≥18 years old and reported injection drug use (IDU) in the past 2 years. Four domains of drug use stigma were examined (internalized, felt/normative, vicarious, and enacted) with 5-6 items/domain. Each subscale had a range of 0-3 with higher scores reflecting greater stigma (Cronbach's α: 0.85-0.92). For each subscale, multivariable logistic regression with a random-intercept for each city was used to estimate adjusted odds ratios (aOR) of active HCV infection (RNA>30 IU/mL). Analyses incorporated RDS-II weights.

**Results:** Of 11,663 participants (median age: 30 years; 94.2% male), 73.1% reported IDU in the past 6 months and 33.8% had active HCV infection. The median score for both the internalized stigma and felt/normative subscales was 1.8; 69.1% endorsed a vicarious stigma item and 39.3% endorsed an enacted stigma item. Reporting any vicarious and enacted stigma was positively associated with a history of needle-sharing (aOR=1.29 [95%CI=1.04-1.59] and aOR=1.52 [95%CI=1.26-1.83], respectively), independent of age, gender, education, homelessness, incarceration, alcohol dependence, and HIV status. PWID reporting any enacted stigma had significantly greater odds of active HCV infection (aOR=1.18 [95%CI=1.04-1.33]), as did PWID with internalized stigma scores in the highest quartile (vs. lowest quartile; aOR=1.62 [95%CI=1.09-2.40]), independent of age, gender, education, homelessness, incarceration, alcohol dependence, frequency of IDU, ever sharing needles, ever participating in medication for opioid use disorder or syringe service programs, and HIV status.

**Conclusion:** PWID reporting enacted and internalized drug use stigma were significantly more likely to be living with HCV infection, suggesting stigma may play a role in HCV transmission and impede efforts to achieve HCV elimination. Strategies to reduce drug use-related stigma and discrimination are warranted.



**Figure. Association of drug use stigmas with active hepatitis C virus infection among PWID in India (n=11,663).** \*\*\* indicates p<0.05

**448 ACCESS TO HCV CARE AMONG HIV/HCV-COINFECTED PEOPLE WHO INJECT DRUGS ACROSS CANADA**

**Charlotte Lanièce Delaunay<sup>1</sup>**, Mathieu Maheu-Giroux<sup>1</sup>, Gayatri Marathe<sup>1</sup>, Sahar Saeed<sup>2</sup>, Curtis Cooper<sup>3</sup>, Sharon Walmsley<sup>4</sup>, Joseph Cox<sup>5</sup>, Mark Hull<sup>6</sup>, Valérie Martel-Laférière<sup>7</sup>, Marina B. Klein<sup>5</sup>

<sup>1</sup>McGill University, Montreal, Canada, <sup>2</sup>Washington University in St Louis, St Louis, MO, USA, <sup>3</sup>University of Ottawa, Ottawa, Canada, <sup>4</sup>University of Toronto, Toronto, Canada, <sup>5</sup>Research Institute of McGill University Health Centre, Montreal, Canada, <sup>6</sup>University of British Columbia, Vancouver, Canada, <sup>7</sup>Centre de Recherche du CHUM, Montreal, Canada

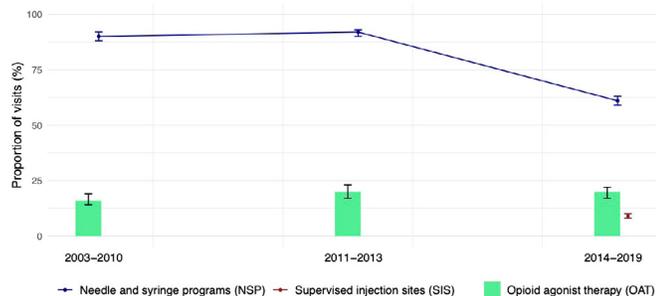
**Background:** In North America, 81% of new HCV infections occur among people who inject drugs (PWID), and coinfection with HIV can exacerbate disease severity. Quantifying unmet needs in HCV prevention and treatment among HIV-HCV coinfecting PWID is key for developing appropriate interventions to eliminate HCV as a public health threat by 2030. We investigated temporal trends in 1) HCV treatment uptake and efficacy; 2) injection practices; and 3) access to harm reduction programs among HIV-HCV coinfecting PWID in Canada from 2003 to 2019.

**Methods:** We used data from the Canadian Coinfection Cohort, a prospective cohort study of 2,004 HIV-HCV coinfecting patients. We included 1,090 participants from Quebec, Ontario, Saskatchewan, and British Columbia who reported injecting at least once between 2003 and 2019. Trends were examined using 3 time periods based on HCV treatment guidelines: 2003-2010: interferon/ribavirin-based; 2011-2013: 1st generation direct-acting antivirals (DAAs); and 2014-2019: 2nd generation DAAs. The harm reduction services assessed include needle and syringe programs (NSP), opioid agonist therapy (OAT), and supervised injection sites (SIS).

**Results:** The participants' median age was 44 years; 69% were male; 33% were Indigenous. The overall HCV treatment rate among HCV RNA-positive people increased from 7 per 100 person-years (PY, 95%CI: 5-9) in 2003-2010 to 20 per 100 PY (95%CI: 18-22) in 2014-2019. In the 2nd generation DAA era, treatment efficacy was >90%, compared to 57% in 2003-2010. Cocaine remained the most frequently injected drug among active PWID, but its consumption decreased from 84% (95%CI: 83-86) of visits in 2003-2010 to 57% (95%CI: 56-59) in 2014-2019. Opioid injection increased from 50% (95%CI: 47-52) of visits in 2003-2010 to 60% (95%CI: 58-61) in 2014-2019. Report of needle/syringe sharing declined from 12% (95%CI: 11-15) in 2003-2010 to 5% (95%CI: 4-6) in 2014-2019, yet paradoxically, report of NSP also decreased (Figure). This might reflect a reduction in number of daily injections due to reduced cocaine use. OAT engagement among opioid injectors was also low (≤20%), with no clear temporal trend. SIS data became available in 2014-2019 (reported at 9% of visits (95%CI: 8-10)).

**Conclusion:** HCV treatment access and outcomes have greatly improved among coinfecting PWID. Yet, exposure to injection-related risks continues and is increasingly related to opioid use. There is a need to maximize access to proven harm reduction strategies to prevent HCV re-infection and overdose.

Access to harm reduction programs in the past 6 months among (i) active people who inject drugs (NSP and SIS) and (ii) opioid injectors (OAT) in the Canadian Coinfection Cohort from 2003 to 2019



#### 449 FREQUENT HBsAg CLEARANCE DURING TENOFOVIR THERAPY IN HIV/ HBV COINFECTION

**Charles Béguelin**<sup>1</sup>, Bernard Surial<sup>1</sup>, Eveline Hofmann<sup>1</sup>, Matthias Cavassini<sup>2</sup>, Huldrych F. Günthard<sup>3</sup>, Manuel Battegay<sup>4</sup>, Enos Bernasconi<sup>5</sup>, Patrick Schmid<sup>6</sup>, Alexandra L. Calmy<sup>7</sup>, Franziska Suter-Riniker<sup>8</sup>, Andri Rauch<sup>1</sup>, Gilles Wandeler<sup>1</sup>, for the Swiss HIV Cohort Study

<sup>1</sup>University Hospital of Bern, Bern, Switzerland, <sup>2</sup>Lausanne University Hospital, Lausanne, Switzerland, <sup>3</sup>University Hospital Zurich, Zurich, Switzerland, <sup>4</sup>University Hospital Basel, Basel, Switzerland, <sup>5</sup>Regional Hospital of Lugano, Lugano, Switzerland, <sup>6</sup>Cantonal Hospital of St Gallen, St Gallen, Switzerland, <sup>7</sup>University Hospitals of Geneva, Geneva, Switzerland, <sup>8</sup>University of Bern, Bern, Switzerland

**Background:** Among persons with hepatitis B virus (HBV)-monoinfection, loss of the hepatitis B surface antigen (HBsAg), also described as HBV functional cure, is a rare event but associated with reduced incidence of liver-related complications. We aimed to assess the proportion of HBV functional cure among persons with HIV/HBV-coinfection during long-term tenofovir-therapy who experienced HBV functional cure, and to evaluate the association between quantitative HBsAg (qHBsAg) levels and this outcome.

**Methods:** All Swiss HIV Cohort Study participants with two positive HBsAg more than 6 months apart, and at least 4 years on tenofovir-containing antiretroviral therapy (ART) were considered. Our main outcomes were the loss of HBsAg during the first 2 years of tenofovir therapy and until the last available follow-up. We explored the association between qHBsAg levels at tenofovir start and HBsAg loss using multivariable logistic regression adjusted for gender, age, ethnicity, HIV transmission group, CD4 count (<350/ $\mu$ l), as well as for HBV suppression (<20 IU/mL) and low qHBsAg (<1000 IU/mL) at tenofovir start.

**Results:** A total of 272 patients were included. Median age was 41 years (IQR 36-46) and 221 (81%) were men. At tenofovir start, 110 (49%) patients were hepatitis B envelope antigen (HBeAg) positive, 229 (84%) had detectable HBV-DNA (median 1050 IU/ml, IQR 89-1.1x10E6) and 21% had low qHBsAg. HBsAg loss was observed in 8% (19/230) of participants during the first 2 years of tenofovir-containing ART and in 16% (43/262) of them after a median follow-up time of 8.4 years (IQR 2.6-15.8). At the last follow up, 54% (16/27) of those with HBsAg loss seroconverted for Anti-HBs antibodies. In multivariable analysis, low qHBsAg at tenofovir start (OR 12.01, CI 2.50-57.71) as well as female gender (OR 9.15, CI 1.08-77.45) were significant predictors of HBsAg loss, whereas this outcome was less likely among participants with negative baseline HBV DNA (OR 0.14, CI 0.02-0.79).

**Conclusion:** We found high rates of HBsAg loss in PLWH coinfecting with HBV on tenofovir-containing ART, and baseline quantitative HBsAg level was a strong predictor of this outcome.

#### 450 HBV REPLICATION DURING TENOFOVIR THERAPY IS FREQUENT IN HIV/ HBV COINFECTION

**Eveline Hofmann**<sup>1</sup>, Bernard Surial<sup>1</sup>, Matthias Cavassini<sup>2</sup>, Huldrych F. Günthard<sup>3</sup>, Manuel Battegay<sup>4</sup>, Enos Bernasconi<sup>5</sup>, Patrick Schmid<sup>6</sup>, Alexandra L. Calmy<sup>7</sup>, Franziska Suter-Riniker<sup>8</sup>, Andri Rauch<sup>1</sup>, Gilles Wandeler<sup>1</sup>, Charles Béguelin<sup>1</sup>, for the Swiss HIV Cohort Study

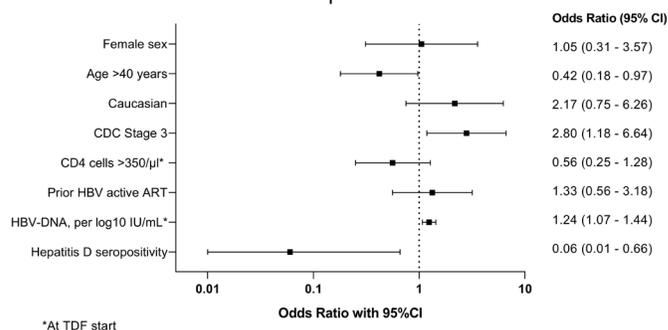
<sup>1</sup>University Hospital of Bern, Bern, Switzerland, <sup>2</sup>University of Lausanne, Lausanne, Switzerland, <sup>3</sup>University Hospital Zurich, Zurich, Switzerland, <sup>4</sup>University Hospital Basel, Basel, Switzerland, <sup>5</sup>Ospedale Regionale di Lugano, Lugano, Switzerland, <sup>6</sup>Cantonal Hospital of St Gallen, St Gallen, Switzerland, <sup>7</sup>University Hospitals of Geneva, Geneva, Switzerland, <sup>8</sup>University of Bern, Bern, Switzerland

**Background:** In persons living with HIV (PLWH) coinfecting with hepatitis B virus (HBV), a tenofovir (TDF) containing antiretroviral therapy (ART) is the treatment of choice. Despite this treatment, certain patients exhibit incomplete HBV suppression. Ongoing viral replication has a negative impact on achieving functional cure, accelerates fibrosis, and is associated with a higher risk of developing hepatocellular carcinoma. In this study, we aimed to describe the proportion of PLWH with persistent HBV replication despite tenofovir and to identify associated risk factors.

**Methods:** We included all PLWH coinfecting with HBV from the Swiss HIV Cohort Study, defined as two positive hepatitis B surface antigen (HBsAg) tests more than 6 months apart, with at least four years of TDF therapy and a positive HBsAg at TDF start. Patients who had an HIV RNA >200 cp/ml at two years were considered to have suboptimal adherence to ART and were therefore excluded from the analyses. We determined the proportion of patients with persistent hepatitis B viremia (HBV DNA  $\geq$ 20 IU/ml) after two years and at the latest follow-up, and explored related risk factors using multivariable logistic regression adjusted for gender, age, ethnicity, CDC Stage 3, CD4 count at TDF start, HBV DNA levels at TDF start, previous HBV treatment, and hepatitis D coinfection.

**Results:** After the exclusion of 21 individuals with replicating HIV and 29 with missing HBV DNA measurements at two years, 222 PLWH were included in our analyses. Median age was 41 years (IQR 36-47), 179 (81%) were men, and median follow-up was 8 years (IQR 5.2-11.0). At TDF start, 187 (84%) had detectable HBV DNA, and 129 (58%) had high-level viremia (HBV DNA >2000 IU/ml). Persistent hepatitis B viremia was present in 61/222 (27%) at two years, and in 39/222 (18%) at the latest follow-up. At two years, 6/61 (10%) patients with persistent hepatitis B viremia had high-level viremia, and 5/39 (13%) at the latest follow-up. In multivariable analysis, persistent hepatitis B viremia at two years was associated with CDC Stage 3 (OR 2.80, CI 1.18-6.64), and high HBV DNA levels at TDF start (OR 1.23, CI 1.07-1.44), whereas it was less likely in individuals with age over 40 years (OR 0.42, CI 0.18-0.97), or with hepatitis D coinfection (OR 0.06, CI 0.01-0.66, Figure).

**Conclusion:** In this nationwide cohort of PLWH coinfecting with HBV, persistent hepatitis B replication after two years of TDF was frequent and associated with HBV DNA levels at TDF start and hepatitis D status.



\*At TDF start  
Figure 1. Forest plot of possible risk factors for persistent hepatitis B viremia (multivariable analysis). Abbreviations: ART=antiretroviral therapy; CDC stage=center for disease control and prevention stage; DNA=deoxyribonucleic acid; HBV=hepatitis B virus, TDF=tenofovir.

#### 451 HEPATITIS B SEROPROTECTION AMONG YOUNG ADULTS LIVING WITH PERINATALLY ACQUIRED HIV

**Florence Bada**<sup>1</sup>, Patrick Ryscavage<sup>1</sup>

<sup>1</sup>University of Maryland, Baltimore, MD, USA

**Background:** The development of protective antibodies against hepatitis B virus (HBV) following vaccination is variable across the HIV population, and has been studied primarily in older adults. HBV seroprotection among young adults

with perinatally-acquired HIV has not been examined. We sought to describe HBV seroprotection among young adults with both perinatally acquired HIV (PHIV) and non-perinatally acquired HIV (NPHIV).

**Methods:** We conducted a retrospective chart review of HBV vaccination history and HBV serology results among young adults ( $\geq 18$  years) with both perinatally acquired HIV and non-perinatally acquired HIV. Bivariable analysis was conducted using Pearson's chi-square, Fisher's exact and t-tests as appropriate to compare the distribution of covariates between PHIV and NPHIV. Multivariable logistic regression was used to determine the odds of having a reactive HBV surface antibody (HBsAb) in PHIV as compared to NPHIV adjusted for CD4 nadir, HIV RNA proximate to the HBsAb test and documentation of HBV vaccination. HBV seroprotection was defined as a documented HBsAb  $\geq 10$  mIU/mL. Patients with evidence of current or past HBV infection were excluded from the analysis.

**Results:** Two hundred individuals (N=95 PHIV, N=105 NPHIV) aged 18–36 years had a recorded HBV serology result (Table 1). The cohort was predominantly Black (96%) and female (55%). PHIV were significantly younger (median age 28 vs. 29 years), had been HIV-infected for longer (28 vs 8 years), had a lower median CD4 nadir (182 vs 404 cells/mm<sup>3</sup>), and were more likely to have achieved HIV viral suppression prior to HBsAb test. In addition, PHIV received more documented HBV vaccine boosters, and were more likely to have documented completion of a 3 shot series (mean # HBV vaccinations: 4.4 among PHIV, 3.1 among NPHIV). Overall HBV seroprotection was 51%, and was lower among PHIV (37.9%) compared to NPHIV (65%). By multivariable logistic regression, the adjusted odds of having a reactive HBsAb was 60% lower in PHIV adults as compared to NPHIV adults (OR .40, 95% CI 0.20–0.82).

**Conclusion:** Hepatitis B seroprotection was low in this cohort of young adults with HIV infection. Adults with perinatally-acquired HIV were less likely to achieve seroprotection despite a high number of total documented vaccinations across time. Providers should assess HBV seroprotection in all HIV-infected young adults, with vigilant attention to seroresponse among PHIV. Novel approaches to HBV immunization should be sought in this population.

Table 1: Demographic and clinical characteristics of the cohort

|   | PHIV<br>N=95       | NPHIV<br>N=105   | P-value |
|---|--------------------|------------------|---------|
| Current Age – median (IQR)                      | 28 (25–31)         | 29 (27–33)       | 0.03    |
| Sex   |                    |                  |         |
| Male  | 39 (41)            | 52 (50)          | 0.23    |
| Female  | 56 (59)            | 53 (51)          |         |
| Race  |                    |                  |         |
| Black   | 93 (98)            | 98 (93)          | 0.17    |
| White   | 2 (2)              | 7 (7)            |         |
| Ethnicity                                       |                    |                  |         |
| Non-Hispanic                                    | 95 (100)           | 102 (97)         | 0.25    |
| Hispanic  | 0 (0)              | 3 (3)            |         |
| Duration of HIV Infection (Years)               | 28.3 (24.9 – 30.6) | 8.3 (5.8 – 10.3) | <.0001  |
| Other Immunosuppressive Condition               |                    |                  |         |
| Yes   | 3 (3)              | 0 (0)            | 0.11    |
| No  | 92 (97)            | 105 (100)        |         |
| CD4 Nadir – median, cells/mm <sup>3</sup> (IQR) | 182 (54–349)       | 404 (276 – 578)  | <.0001  |
| HIV RNA proximate to HBsAb, cpm                 |                    |                  |         |
| $\leq 200$                                      | 44 (46)            | 36 (34)          | 0.0040  |
| 200 – $\leq 1000$                               | 10 (11)            | 3 (3)            |         |
| $> 1000$  | 31 (33)            | 59 (56)          |         |
| Missing   | 10 (11)            | 7 (7)            |         |
| Most recent RNA, cpm                            |                    |                  |         |
| $\leq 200$                                      | 61 (64)            | 76 (72)          | 0.19    |
| 200 – $\leq 1000$                               | 3 (3)              | 6 (6)            |         |
| $> 1000$  | 31 (33)            | 23 (22)          |         |
| Documented HBV Vaccination                      |                    |                  |         |
| Yes   | 90 (95)            | 75 (71)          | <.00001 |
| No  | 5 (5)              | 30 (29)          |         |
| At least one booster dose beyond initial series |                    |                  |         |
| Yes   | 33 (35)            | 16 (15)          | 0.0014  |
| No  | 62 (65)            | 89 (85)          |         |
| sAb reactive ( $\geq 10$ mIU/mL)                |                    |                  |         |
| Yes   | 34 (36)            | 68 (65)          | <.0001  |
| No  | 61 (64)            | 37 (35)          |         |

PHIV: perinatally acquired HIV; NPHIV: non-perinatally acquired HIV; cpm: copies per milliliter; HBV: hepatitis B virus; sAb: hepatitis B surface antibody

## 452 HEPATITIS DELTA INFECTIONS AMONG PERSONS WITH HIV IN EUROPE

Charles Béguelin<sup>1</sup>, Andrew Atkinson<sup>1</sup>, Anders Boyd<sup>2</sup>, Karolin Falconer<sup>3</sup>, Nikolai Kirkby<sup>4</sup>, Franziska Suter-Riniker<sup>5</sup>, Huldrych F. Günthard<sup>6</sup>, Jürgen K. Rockstroh<sup>7</sup>, Amanda Mocroft<sup>8</sup>, Andri Rauch<sup>1</sup>, Lars Peters<sup>4</sup>, Gilles Wandeler<sup>1</sup>, for the EuroSIDA and SHCS Study

<sup>1</sup>University Hospital of Bern, Bern, Switzerland, <sup>2</sup>Public Health Service Amsterdam, Amsterdam, Netherlands, <sup>3</sup>Karolinska University Hospital, Stockholm, Sweden, <sup>4</sup>Rigshospitalet, Copenhagen, Denmark, <sup>5</sup>University of Bern, Bern, Switzerland, <sup>6</sup>University Hospital Zurich, Zurich, Switzerland, <sup>7</sup>Bonn University Hospital, Bonn, Germany, <sup>8</sup>Institute for Global Health UCL, London, United Kingdom

**Background:** A high prevalence of hepatitis delta virus (HDV) infection, the most severe form of viral hepatitis, has been reported among persons with HIV (PWH) and hepatitis B virus (HBV) infection in European cohorts. We analyzed data from two large HIV cohorts to characterize the current epidemiological trends in HDV infections across Europe.

**Methods:** All PWH with a positive hepatitis B surface antigen (HBsAg) test in the Swiss HIV cohort Study and EuroSIDA were considered and tested for anti-HDV antibodies. HDV RNA amplification was performed in anti-HDV-positive patients. Demographic and clinical characteristics at initiation of antiretroviral therapy were compared between HDV-positive and HDV-negative individuals using descriptive statistics. The associations between HDV infection and overall mortality, liver-related mortality as well as hepatocellular carcinoma (HCC) were assessed using Kaplan–Meier and multivariable Cox regression adjusted for age, gender, HIV transmission group, baseline CD4 and cohort.

**Results:** Of 2793 HBsAg-positive patients, 1556 (56%) had stored serum available and were included. The prevalence of HDV co-infection was 15.2% (237/1556, 95% CI: 13.5%–17.1%), of whom 66% (132/200) had active HDV replication. Anti-HDV antibody positive prevalence ranged from 32.8% (95% CI: 24.7%–41.7%) in Eastern Europe, to 29.7% (95% CI: 21.4%–39.1%) in the South and 14.9% (95% CI: 12.7%–17.4%) in Northwestern Europe. HDV-positive persons were more likely to be persons who inject drugs (PWID) (76.8% vs 14.3%,  $p < 0.001$ ) and to have positive hepatitis C serology (75.5% vs. 24.3%,  $p < 0.001$ ), compared to those without HDV-infection. Among PWID, the prevalence of HDV co-infection was 49.2%, with similar estimates across the three regions. During a median follow-up time of 9.8 years [IQR 4–16.6], seventy-five (31.6%) HDV-positive patients and 261 (19.8%) HDV-negative individuals died. 43% (32/75) of the deaths were liver related in HDV-positive patients compared to 18% (46/261) in HDV-negative individuals. HDV infection was associated with overall mortality (adjusted hazard ratio 1.4; 95% CI 1.1–1.95,  $p = 0.03$ ), liver-related death (2.9, 1.6–5.1,  $p < 0.001$ ) and hepatocellular carcinoma (6.5, 2.6–16.6,  $p < 0.001$ ).

**Conclusion:** Hepatitis delta prevalence among PWH in Europe varies strongly across regions and is particularly high in PWIDs. This could reflect different availability of harm reduction programs. HDV coinfection is associated with increased mortality and liver related events including HCC.

## 453 RPV ACTIVATES STAT1 IN STELLATE CELLS TO REGULATE LIVER INJURY IN PLWHIV AND NAFLD

Maria Luisa Montes<sup>1</sup>, Carmen Busca Arenzana<sup>1</sup>, Angela B. Moragrega<sup>2</sup>, Nadezda Apostolova<sup>2</sup>, Antonio Oliveira<sup>1</sup>, Luz Martin Carbonero<sup>1</sup>, Eulalia Valencia<sup>1</sup>, Victoria Moreno<sup>1</sup>, Jose I. Bernardino<sup>1</sup>, Ignacio Perez-Valero<sup>1</sup>, Juan González-García<sup>1</sup>, Juan V. Espulges<sup>3</sup>, Jose R. Arribas<sup>1</sup>, Ana Blas-García<sup>4</sup>

<sup>1</sup>Hospital La Paz Institute for Health Research, Madrid, Spain, <sup>2</sup>Departamento de Farmacología, Facultad de Medicina, Universidad de Valencia, Valencia, Spain, <sup>3</sup>Departamento Farmacología, Departamento de Fisiología, Facultad de Medicina, Universidad de Valencia, Valencia, Spain, <sup>4</sup>Departamento de Fisiología, Facultad de Medicina, Universidad de Valencia, Valencia, Spain

**Background:** In vitro experiments and analysis of different murine models of chronic liver disease have recently shown Rilpivirine (RPV) selectively triggers hepatic stellate cell (HSC) inactivation and apoptosis through signal transducer and activator of transcription (STAT)1-mediated pathways. These actions clearly attenuate liver inflammation and fibrosis, regardless of the etiology of liver injury. We studied the effects of this NNRTI on hepatic steatosis, inflammation and fibrosis in liver biopsies of HIV-infected subjects with identified NAFLD.

**Methods:** In a cross-sectional study, we analyzed 42 well-controlled PLWHIV subjects diagnosed with NAFLD by liver biopsy. Histological analysis was performed in 5 $\mu$ m paraffin-embedded liver sections by H&E staining and immunohistochemistry. Nuclear expression of STAT-1 was quantified and compared between subjects with and without RPV-based therapy. A log

transformation (Ln) of the STAT-1 values was applied. Differences in LnSTAT-1 was analyzed by factorial analysis of variance, considering exposure to RPV and diagnoses of steatosis, steatohepatitis and fibrosis as inter-subject factors, and exposure time to RPV and BMI as covariates.

**Results:** Studied subjects were 100% male, median age 49 (44-54) years, median CD4 count 802 (608-940) cells/ L, and 60% of them had metabolic syndrome. All subjects were receiving ART with undetectable HIV viral load and 45% were receiving RPV-based therapy. Liver biopsies showed 43% steatosis >30%, 60% steatohepatitis and 43% fibrosis F>1. Detection of nuclear STAT1 expression in non-parenchymal cells revealed a significant association of RPV-based therapy with enhanced activation of this transcription factor in hepatic sections of patients with identified liver injury. The protective effect of promoting STAT1-dependent HSC inactivation was observed in patients with different stages of NAFLD, from mild/intense steatosis to steatohepatitis or fibrosis. Interestingly, the increase in STAT1 activation observed in those exposed to RPV-based therapy was also evident in FO subjects, probably due to the presence of steatosis or steatohepatitis among these subjects

**Conclusion:** PLWHIV with NAFLD who receive RPV-based therapy showed increased STAT1 activation, pointing to ongoing HSC inactivation and apoptosis to reduce the progression of hepatic damage. Our results suggest RPV-based ART would be especially indicated in HIV-infected patients with NAFLD-derived liver injury to prevent liver fibrosis and inflammation.

Table 1

|                 |     |                 | LnSTAT-1         | LnSTAT-1                 | P     |
|-----------------|-----|-----------------|------------------|--------------------------|-------|
|                 |     |                 | Mean (CI 95%)    | Mean difference (CI 95%) |       |
| Steatosis > 30% | No  | RPV non-exposed | 9.2 (8.2; 10.2)  | 1.12 (-0.50; 2.74)       | 0.17  |
|                 |     | RPV exposed     | 10.3 (9.3; 11.3) |                          |       |
|                 | Yes | RPV non-exposed | 8.9 (7.9; 9.9)   | 2.06 (0.25; 3.87)        |       |
|                 |     | RPV exposed     | 10.9 (9.7; 12.2) |                          |       |
| Steatohepatitis | No  | RPV non-exposed | 9.7 (8.5; 10.8)  | 0.5 (-0.8; 1.7)          | 0.447 |
|                 |     | RPV exposed     | 10.2 (9.1; 11.3) |                          |       |
|                 | Yes | RPV non-exposed | 8.8 (8.0; 9.7)   | 2.07 (0.46; 3.67)        |       |
|                 |     | RPV exposed     | 10.9 (9.8; 12.0) |                          |       |
| Fibrosis ≥ F1   | No  | RPV non-exposed | 9.0 (8.2; 9.9)   | 1.66 (0.21; 3.11)        | 0.03  |
|                 |     | RPV exposed     | 10.7 (9.7; 11.7) |                          |       |
|                 | Yes | RPV non-exposed | 8.9 (7.8; 9.9)   | 1.77 (0.02; 3.53)        |       |
|                 |     | RPV exposed     | 10.6 (9.5; 11.7) |                          |       |

\* Marginal mean (95% CI) adjusted for exposure time to RPV (months) and BMI

#### 454 RELATIONSHIP BETWEEN ALCOHOL USE AND SUSTAINED VIROLOGIC RESPONSE TO HCV DAA THERAPY

**Emily J. Cartwright**<sup>1</sup>, Chloe Pierret<sup>2</sup>, Christopher T. Rentsch<sup>2</sup>, Caroline Minassian<sup>2</sup>, Janet P. Tate<sup>3</sup>, David A. Fiellin<sup>3</sup>, Amy Justice<sup>3</sup>, Vincent Lo Re<sup>4</sup>

<sup>1</sup>Atlanta VA Medical Center, Decatur, GA, USA, <sup>2</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>3</sup>Yale University, New Haven, CT, USA, <sup>4</sup>University of Pennsylvania, Philadelphia, PA, USA

**Background:** Some payors include alcohol abstinence as a requirement for reimbursement of direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection. However, it remains unclear if alcohol use is associated with lower likelihood of sustained virologic response (SVR) to DAA therap. We examined the relationship between alcohol use, assessed within the 18 months prior to DAA therapy, and SVR.

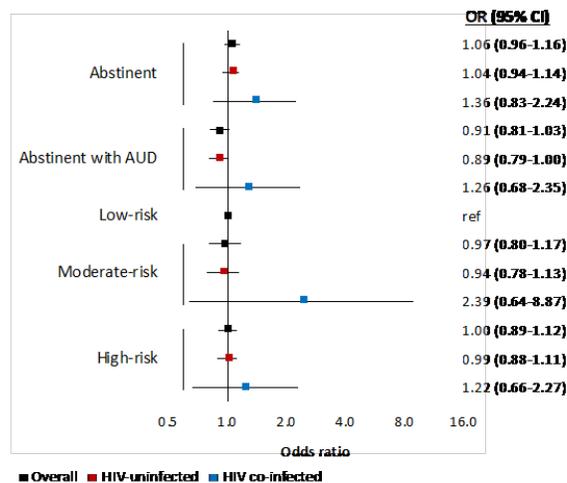
**Methods:** Using the Veterans Health Administration (VA) Birth Cohort, which includes all Veterans born between 1945 and 1965, we identified HCV patients dispensed DAA therapy between 1 January 2014 and 31 December 2018. Alcohol use (abstinent, abstinent with history of alcohol use disorder [AUD], lower risk, moderate risk, high risk) was determined using a combination of self-reported score from the Alcohol Use Disorders Identification Test-Consumption instrument and validated International Classification of Diseases, 9th/10th Revision AUD diagnoses. We assessed SVR, defined as undetectable HCV RNA ≥12 weeks after DAA therapy, through May 31, 2019. Multivariable logistic regression was used to determine odds ratios (ORs) with 95% confidence intervals (CIs) of SVR for each alcohol use category compared to lower risk, adjusting for HCV genotype, HBV coinfection, and hepatic decompensation. A stratified analysis was performed by HIV status.

**Results:** Among 77,046 HCV patients dispensed DAA therapy (mean age, 63 years; 97% male; 50% white race; 83% HCV genotype 1; 3% HIV positive), alcohol use prior to DAA therapy varied: abstinent (47%), abstinent with AUD (13%) lower risk (19%), moderate risk (5%), and high risk (17%). Overall, 94% of patients achieved SVR. We observed no association with SVR among patients whose alcohol use was classified as abstinent (OR 1.06, 95% CI 0.96-1.16), abstinent with history of AUD (OR 0.91, 95% CI 0.81-1.03), moderate risk (OR 0.97, 95% CI 0.8-1.17), or high risk (OR 1.00, 95% CI 0.89-1.12) relative to lower

risk alcohol use (Figure). Results were similar when stratified by HIV status; however, the HIV co-infected subset (n=2,372), was underpowered.

**Conclusion:** Level of alcohol use, even at the highest category of use, was not associated with a lower likelihood of achieving SVR after adjusting for important differences between the groups. These findings suggest that DAA therapy should be provided and reimbursed despite alcohol use. Restricting access to DAA therapy based on alcohol use is an unnecessary barrier to DAA therapy and challenges HCV elimination goals.

Figure. Adjusted associations between alcohol category and SVR



#### 455 APPLICATION OF THE NOVEL FIBROSCAN-AST SCORE IN AN HIV-MONOAFFECTED COHORT

**Jenny Bischoff**<sup>1</sup>, Wenyi Gu<sup>2</sup>, Christoph Boesecke<sup>1</sup>, Jan-Christian Wasmuth<sup>1</sup>, Carolynne Schwarze-Zander<sup>1</sup>, Kathrin Van Bremen<sup>1</sup>, Raphael Mohr<sup>1</sup>, Jonel Trebicka<sup>2</sup>, Jürgen K. Rockstroh<sup>1</sup>

<sup>1</sup>Bonn University Hospital, Bonn, Germany, <sup>2</sup>University Hospital Frankfurt, Frankfurt, Germany

**Background:** Non-alcoholic fatty liver disease (NAFLD) is becoming a serious complication for people living with HIV (PLWH). With validation of transient elastography (TE) and controlled attenuation parameter (CAP) as non-invasive tools in contrast to biopsies, diagnosing liver fibrosis and hepatic steatosis (HS) had become much easier. Quite recently the FibroScan-AST (FAST) score had been validated in HIV negative individuals with suspected NAFLD as an efficient tool to identify those at risk of progression to NASH. To date the FAST score had not been reported in HIV mono-infected individuals (HIV+).

**Methods:** We enrolled 432 HIV positive patients presenting at our outpatient clinic between August 2013 to December 2018. Liver stiffness and HS were assessed yearly by TE using an M-probe of FibroScan (Echosens, Paris, France). FAST Score was calculated retrospectively according to Newsome et al. for each year and compared to other markers of liver disease.

**Results:** Overall, 303 HIV+ patients (79% male, average age at baseline 45.9±11.5 years, average duration of infection 9.3±6.4 years) with at least two visits were analysed. All patients were administered ART. FAST score was available for 187, 236, 222, 192 and 111 patients at visit V1, V2, V3, V4 and V5, respectively. Distribution of FAST Score and CAP values are shown in Fig. 1. FAST score at baseline showed a strong correlation with baseline FIB4 scores (R: 0.740; p<0.001) and APRI scores (R: 0.514; p<0.001) but was weaker with CAP values (R: 0.385; p<0.001). In contrast to HIV specific parameters (baseline viral suppression, nadir CD4 count <200/μl), male sex, ever being treated with an InSTI and a baseline BMI >25kg/m<sup>2</sup> as well as Diabetes mellitus type 2 (DM2) were associated with higher FAST scores.

**Conclusion:** This is the first report on FAST Score in HIV+ persons. We found a significant correlation with FIB4, APRI and CAP values. In contrast to an observed steady redistribution towards higher CAP values (reflecting an increase in steatosis) over five years, the FAST score remained nearly unchanged in its distribution until there was a sudden increase towards a so far not well defined "grey area" of progressive NAFLD after four years of observation. Possible risk factors in univariable analyses for higher FAST scores were male sex, overweight, DM2 and certain antiretroviral drugs. Due to the rapid,

inexpensive and non-invasive assessment of the FAST score, it should be further investigated in PLWH.

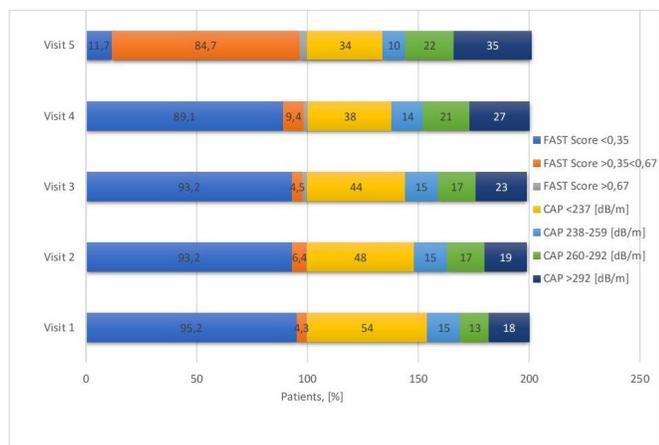


Fig. 1: FAST Score and CAP value [dB/m] distribution for each year in HIV+ individuals; FAST Score <0,35 defined as rule out for NASH, FAST Score >0,35<0,67 defined as grey area, FAST Score >0,67 defined as rule in NASH; CAP <237 [dB/m] defined as no steatosis, CAP 238-259 [dB/m] defined as S1 Steatosis, CAP 260-292 [dB/m] defined as S2 Steatosis, CAP >292 [dB/m] defined as S3 Steatosis;

FAST score V1 vs V5 p=0,63, V2 vs V5 p=0,75, V3 vs V5 p=0,033, V4 vs V5 p<0,001; CAP V1 vs V5 p=0,008 V2/V3/V4 vs V5 p<0,001

#### 456 ARE MODERN ANTIRETROVIRALS HEPATOTOXIC? SIGNALS IN PATIENTS STARTING ART IN NA-ACCORD

**Marina B. Klein**<sup>1</sup>, James Young<sup>2</sup>, Keri N. Althoff<sup>3</sup>, Edward R. Cachay<sup>4</sup>, Ricardo Franco<sup>5</sup>, M John Gill<sup>6</sup>, Michael A. Horberg<sup>7</sup>, Mark Hull<sup>8</sup>, H. Nina Kim<sup>9</sup>, Vincent Lo Re<sup>10</sup>, Richard Moore<sup>11</sup>, Jennifer Price<sup>12</sup>, Giada Sebastiani<sup>1</sup>, Michael J. Silverberg<sup>13</sup>, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

<sup>1</sup>McGill University Health Centre, Montreal, Canada, <sup>2</sup>McGill University, Montreal, Canada, <sup>3</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>4</sup>University of California San Diego, San Diego, CA, USA, <sup>5</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>6</sup>Southern Alberta Clinic, Calgary, Canada, <sup>7</sup>Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA, <sup>8</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, <sup>9</sup>University of Washington, Seattle, WA, USA, <sup>10</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>11</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>12</sup>University of California San Francisco, San Francisco, CA, USA, <sup>13</sup>Kaiser Permanente Northern California, Oakland, CA, USA

**Background:** Despite effective antiretroviral therapy (ART), rates of end-stage liver disease (ESLD) remain high. Specific ART drugs may add to the risk of ESLD but past analyses have studied prevalent users exposed to old hepatotoxic drugs and used inadequate methods for detecting risk signals in complex data. We sought to detect which components of modern ART might contribute to ESLD risk.

**Methods:** We selected patients from 12 cohorts contributing validated ESLD events to the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). We followed those initiating ART after 1 Jan 2004 with a nucleos(t)ide backbone of either abacavir/lamivudine or tenofovir/emtricitabine and a modern third (anchor) drug until a first ESLD event, death, end of a cohort's ESLD validation period, loss to follow up or 31 Dec 2015. We estimated associations between cumulative exposure to each drug (per five years) and ESLD using a Bayesian Cox model akin to the FDA's method for detecting signals in MedWatch data. To minimise the risk of false positives given multiple exposures and few events, we fitted a hierarchical model asserting weakly informative prior distributions based on past studies. The model allowed for variation between cohorts in the baseline hazard and included covariates for alcohol abuse, hepatitis B (HBV) and C (HCV) status, FIB-4 fibrosis score when starting ART and time updated detectable HIV RNA and CD4 cell count.

**Results:** Of the 10,564 patients included, 62 had a validated ESLD event (42 ascites, 10 hepatic encephalopathy, 7 variceal hemorrhage, 3 hepatocellular carcinoma). Incidence rates (per 1000 patient years) were: 0.4 in HIV-monoinfected, 2.8 in HIV/HBV, 7.2 in HIV/HCV and 13.1 in HIV/HBV/HCV-coinfected patients. Comparing prior and posterior hazard ratios (HR), and their

95% credible intervals (CrI), shows the data contain little information about the risk associated with integrase inhibitors – prior and posterior intervals are similar (Table). Both backbones and efavirenz show no signs of liver toxicity. Of the nine anchor drugs, boosted atazanavir and darunavir have the strongest signals. By comparison, HCV was obviously harmful (HR 4.4, 95% CrI 2.8 to 7.2). **Conclusion:** We show how new user cohort designs can be used to detect toxicity signals even with relatively few events. While modern ART poses less risk for ESLD than hepatitis coinfection, some drugs showed toxicity signals. Confirming whether these drugs contribute to ESLD risk requires designs that focus on causality.

**Table** Prior and posterior hazard ratios (HR) and their credible intervals (CrI) for cumulative exposure to each antiretroviral drug component (per five years).

| Drug class                                      | Component    | Prior HR |             | Posterior HR |             |
|---|--------------|----------|-------------|--------------|-------------|
|   |              | Median   | 95% CrI     | Median       | 95% CrI     |
| Boosted protease inhibitors                     | Atazanavir   | 1.5      | 0.32 to 7.1 | 1.8          | 0.82 to 3.9 |
|   | Darunavir    | 1.5      | 0.32 to 7.1 | 2.0          | 0.86 to 4.7 |
|   | Lopinavir    | 1.5      | 0.32 to 7.1 | 1.5          | 0.56 to 3.7 |
| Non-nucleoside reverse-transcriptase inhibitors | Efavirenz    | 1.5      | 0.32 to 7.1 | 1.1          | 0.49 to 2.5 |
|   | Nevirapine   | 1.5      | 0.32 to 7.1 | 1.5          | 0.51 to 4.2 |
|   | Rilpivirine  | 1.5      | 0.32 to 7.1 | 1.5          | 0.50 to 4.1 |
| Integrase inhibitors                            | Elvitegravir | 1.0      | 0.21 to 4.7 | 1.3          | 0.34 to 4.3 |
|   | Dolutegravir | 1.0      | 0.21 to 4.7 | 1.2          | 0.32 to 4.1 |
|   | Raltegravir  | 1.0      | 0.21 to 4.7 | 1.3          | 0.34 to 3.8 |
| Nucleos(t)ide backbones                         | Abacavir     | 1.0      | 0.25 to 4.0 | 0.95         | 0.39 to 2.3 |
|   | Tenofovir    | 1.0      | 0.25 to 4.0 | 0.78         | 0.36 to 1.8 |

#### 457 IMPACT OF BINGE DRINKING ON MORTALITY AND LIVER DISEASE IN THE SWISS HIV COHORT STUDY

**Bernard Surial**<sup>1</sup>, Nicolas Bertholet<sup>2</sup>, Jean-Bernard Daeppen<sup>2</sup>, Katharine E. Darling<sup>3</sup>, Alexandra Calmy<sup>3</sup>, Huldrych F. Günthard<sup>4</sup>, Marcel Stöckle<sup>5</sup>, Enos Bernasconi<sup>6</sup>, Patrick Schmid<sup>7</sup>, Andri Rauch<sup>1</sup>, Hansjakob Furrer<sup>1</sup>, Gilles Wandeler<sup>1</sup>, for the Swiss HIV Cohort Study

<sup>1</sup>University Hospital of Bern, Bern, Switzerland, <sup>2</sup>Lausanne University Hospital, Lausanne, Switzerland, <sup>3</sup>University Hospitals of Geneva, Geneva, Switzerland, <sup>4</sup>University Hospital Zurich, Zurich, Switzerland, <sup>5</sup>University Hospital Basel, Basel, Switzerland, <sup>6</sup>Servizio di Malattie Infettive, Lugano, Switzerland, <sup>7</sup>St Gallen Cantonal Hospital, St Gallen, Switzerland

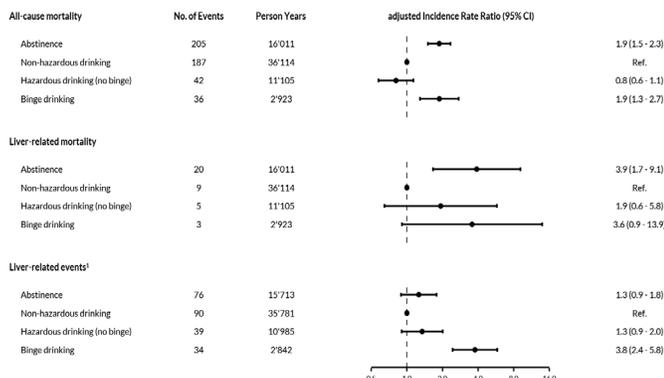
**Background:** Studies in the general population suggest that binge drinking is associated with an increased risk of death independently of the average daily consumption of alcohol. Considering the high prevalence of alcohol use disorder among persons with HIV, we assessed the impact of specific drinking patterns on mortality and the occurrence of liver events in the Swiss HIV Cohort Study.

**Methods:** We included all cohort participants with follow-up between January 2013 and April 2020. Based on responses to the routinely recorded Alcohol Use Disorder Identification Test (AUDIT-C), their drinking behavior was grouped into "abstinence" (no alcohol consumption), "non-hazardous drinking", "hazardous but not binge drinking (AUDIT-C ≥3 in women and ≥4 in men)", and "binge drinking" (≥6 drinks/occasion more than monthly). We estimated adjusted incidence rate ratios (IRR) of all-cause mortality, liver-related mortality and liver events (including the development of cirrhosis) for time-varying drinking patterns using multivariable quasi-Poisson regression, adjusted for demographic characteristics, comorbidities, smoking and illicit drug use.

**Results:** We included 11'849 individuals: 3'264 (27.5%) were female, median age was 46 years (IQR 38–53), 9'097 (76.8%) were Caucasian, 5'425 (45.8%) were men who have sex with men, 573 (4.8%) had hepatitis B coinfection and 1'116 (9.4%) hepatitis C coinfection. Over a median follow-up of 6.8 years (IQR 4.1–7.0), 470 individuals died (incidence rate [IR] 7.1/1'000 person-years [PY], 95% CI 6.5–7.8), of which 37 were liver-related (IR 0.6/1'000 PY, 95% CI 0.4–0.8), and 239 liver events occurred (IR 3.7/1'000 PY, 95% CI 3.2–4.2). Compared to non-hazardous drinking, binge drinking was associated with a higher rate of all-cause mortality (adjusted IRR 1.9, 95% CI 1.3–2.7) and liver events (adjusted IRR 3.8, 95% CI 2.4–5.8). All-cause (adjusted IRR 1.9, 95% CI 1.5–2.3) and liver-

related mortality (adjusted IRR 3.9, 95% CI 1.7–9.1) were increased in individuals reporting abstinence compared to non-hazardous drinking. We observed no significant differences in outcome rates between non-hazardous and hazardous without binge drinking (Figure). Findings were consistent after excluding individuals with viral hepatitis.

**Conclusion:** Among persons with HIV in Switzerland, binge drinking was associated with all-cause mortality and the incidence of liver events, highlighting the importance of assessing alcohol drinking patterns to identify individuals most at risk for complications.



**Figure:** Impact of alcohol drinking pattern on all-cause mortality, liver-related mortality and liver-related events. Analyses on all-cause mortality were adjusted for age, sex, education level, ethnicity, HIV transmission group, infection with hepatitis B or C, history of AIDS defining disease, smoking, any illicit drug use, presence of depression, employment status, and whether individuals lived together with a partner or not. Covariates for liver-related mortality included age, sex, and viral hepatitis coinfection, and analyses for liver events were adjusted for the same covariates as the analysis on overall mortality, with the addition of time-varying values of body mass index. <sup>1</sup>Liver events included cirrhosis based on confirmed APRI >2 or histology, diagnosis of portal hypertension, hepatocellular carcinoma, variceal bleeding, hepatic encephalopathy stage III or IV, hepatorenal syndrome, spontaneous bacterial peritonitis and ascites confirmed on imaging.

#### 458 HIV/HCV COINFECTION INDUCES PRO-INFLAMMATORY PLASMA GLYCOMIC SIGNATURES

Jenny Pena Dias<sup>1</sup>, Leila B. Giron<sup>2</sup>, Jane Koshy<sup>2</sup>, Damani A. Piggott<sup>3</sup>, Mohamed Abdel-Mohsen<sup>2</sup>, Todd Brown<sup>4</sup>

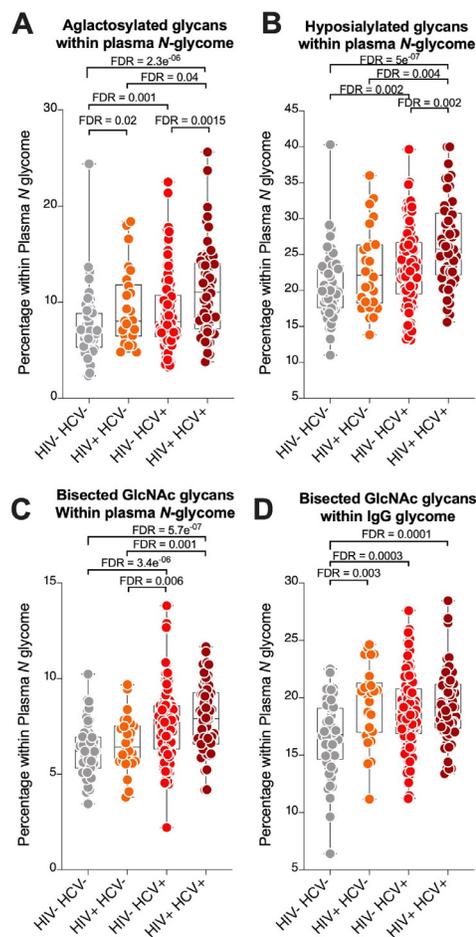
<sup>1</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>The Wistar Institute, Philadelphia, PA, USA, <sup>3</sup>Johns Hopkins University, Baltimore, MD, <sup>4</sup>Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda

**Background:** Glycans on circulating (plasma) glycoproteins and antibodies (IgGs) play an important role in regulating inflammatory responses. In particular, reductions in IgG galactosylation (agalactosylation; loss of the monosaccharide galactose) and sialylation (hypo-sialylation; loss of sialic acid) as well as induction of bisected GlcNAc glycans, increase the pro-inflammatory function of IgGs, by enhancing FcγR binding. These glycomic features have been linked to the development and maintenance of several inflammatory diseases. However, their levels during HIV/HCV co-infection remain unclear.

**Methods:** We enrolled 249 HCV-exposed (HCV antibody positive) adults mean age 56±6 years, 36% female, with and without active HIV and/or active HCV infection in four groups: (52 HCV-/HIV-; 26 HCV-/HIV+; 113 HCV+/HIV-; and 58 HCV+/HIV+), from the AIDS Linked to the IntraVenous Experience (ALIVE) cohort. N-glycans from plasma and isolated IgG were analyzed using capillary electrophoresis. Kruskal-Wallis test was used for statistical analysis. False discovery rate (FDR) was calculated using the Benjamini Hochberg approach to adjust for multiple comparisons.

**Results:** HCV mono-infection was associated with inductions in levels of pro-inflammatory glycomic traits (agalactosylated, hyposialylated, and bisected GlcNAc glycans) in plasma glycoproteins (FDR<0.002) compared to the HCV-/HIV- group (Figure A-C). Furthermore, HCV infection was associated with higher levels of the pro-inflammatory bisected GlcNAc glycans on IgG glycome (FDR=0.0003), compared to the HCV-/HIV- group (Figure D). HIV/HCV co-infection further increased these pro-inflammatory glycomic traits on plasma glycoproteins and IgG when compared to mono-infection and the HCV-/HIV- group (FDR<0.002) (Figure D).

**Conclusion:** We identified novel host glycomic factors that may contribute to higher inflammation and immune activation during HCV/HIV co-infection. The potential prognostic and functional significance of these glycomic signatures in modulating the disease course during HCV/HIV co-infection warrants further investigation.



#### 459 MITOCHONDRIAL DNA HAPLOGROUPS AND SPONTANEOUS HCV CLEARANCE: A MULTI-COHORT ANALYSIS

Todd Hulgan<sup>1</sup>, Candelaria Vergara<sup>2</sup>, David Samuels<sup>3</sup>, Priya Duggal<sup>2</sup>, Arthur Y. Kim<sup>4</sup>, for the HCV Genetics Consortium

<sup>1</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Vanderbilt University, Nashville, TN, USA, <sup>4</sup>Massachusetts General Hospital, Boston, MA, USA

**Background:** Hepatitis C virus (HCV) infects >70 million persons globally. Most persons with HCV have chronic infection and an increased risk of cirrhosis and its complications; a minority spontaneously clear infection. Polymorphisms in interferon lambda (including rs368234815, ΔG/TT) and other genes are estimated to explain ~15% of the variation in HCV spontaneous clearance (SC). Because mitochondria can regulate activation, differentiation, and survival of immune cells, we asked whether mitochondrial DNA (mtDNA) haplogroups were associated with SC in persons with and without HIV co-infection

**Methods:** Data were from the HCV Genetics Consortium, a multi-cohort consortium including individuals of European (EA) and African (AA) genetic ancestry from 15 cohorts across North America and Europe. SC was defined as the presence of HCV antibody without HCV RNA in plasma. Genotyping was performed using the Illumina Omni1-Quad array and 24 mtDNA variants and HaploGrep were used to define haplogroups. In each ancestry group, we performed logistic regression analyses of mtDNA haplogroups and SC, both with stratification by HIV status and including HIV status as a covariate in separate models. Regression models also adjusted for rs368234815 and sex.

**Results:** The total sample included 2028 persons (1581 EA; 447 AA) with HCV. Within the ancestry groups, 68% and 48% were male, 16% and 50% had HIV co-infection, and 37% and 38% had SC, respectively. Overall haplogroup distribution was as expected for EA and AA populations. No statistically significant associations between haplogroups and SC among persons with HCV mono-infection were found. Among EA persons with HCV/HIV co-infection, mtDNA haplogroup I was more frequent in SC independent of rs368234815 and sex (6.8% vs.1.9%; adjusted OR 4.3; 95% CI 1.1-21.3, p=0.04). In models

including all EA persons with HCV and adjusting for HIV co-infection and sex, haplogroup I remained associated with SC (3.9% vs. 2.0%, adjusted OR 2.0; 95% CI:1.1-3.7, p=0.03).

**Conclusion:** In EA persons with HCV/HIV co-infection, a rare mtDNA haplogroup (~3%) was associated with HCV SC. Limitations included small sample sizes for non-EA and HIV co-infection analyses, limited mtDNA variants, and few covariates. While this finding cannot explain substantial SC variation at a population level, it does suggest mitochondrial mechanisms of SC that may be influenced by HIV co-infection. This association should be validated in other cohorts, and mechanisms explored in translational studies.

**460 A SERIAL COMBINATION OF STEATOSIS NONINVASIVE MARKERS IN HIV-MONONINFECTED SUBJECTS**

**Carmen Busca<sup>1</sup>**, Matilde Sanchez-Conde<sup>2</sup>, Marta Rosas<sup>2</sup>, Eulalia Valencia<sup>1</sup>, Ana María Moreno-Zamora<sup>2</sup>, Victoria Moreno<sup>1</sup>, Luz Martín-Carbonero<sup>1</sup>, Santiago Moreno<sup>2</sup>, Ignacio Perez-Valero<sup>1</sup>, Jose I. Bernardino<sup>1</sup>, Jose R. Arribas<sup>1</sup>, Juan González-García<sup>1</sup>, Antonio Olveira<sup>1</sup>, Maria Luisa Montes<sup>1</sup>

<sup>1</sup>Hospital La Paz Institute for Health Research, Madrid, Spain, <sup>2</sup>Hospital Ramón y Cajal, Madrid, Spain

**Background:** Non-alcohol fatty liver disease (NAFLD) is one of the major non-AIDS-defining conditions in people with HIV (PWH), however, the diagnosis is not simple and routine screening for this condition is not well incorporated in their care. Properly validated tests and easy to apply are needed in this population in order to identify people at risk of developing chronic liver disease. Our objective was the validation of non-invasive markers for the diagnosis of NAFLD in HIV-infected patients.

**Methods:** Prospective cohort study of PWH on stable ART regimen and persistent liver enzymes elevation without known liver disease. Whole blood lab test, abdominal ultrasound (US), transient elastography (including CAP) and steatosis and fibrosis non-invasive markers (TyG, HSI, FLI, FIB-4 and APRI) were performed in all participants. A liver biopsy was offered to all patients and performed in those who consented. AUROC analysis was performed to estimate the diagnostic accuracy of non-invasive tests of both steatosis and fibrosis compared to liver biopsy. An algorithm with serial combination of tests was developed.

**Results:** A total of 146 patients were included: 91% men, CDC C3 stage 14.5%, HIV RNA < 50 cop/mL 100%, median (IQR) age 49 years (41-54), BMI 27 (24-30), baseline CD4+ 740 cel/μL (593-930). Metabolic syndrome was diagnosed in 41% and diabetes mellitus or impaired fasting glucose in 43%. Medium values for transaminases were: ALT 50 IU/L (41-77), AST 36 IU/L (28-43), GGT 47 IU/L (30.5-98). Sixty-nine liver biopsies were performed, finding: any degree of steatosis in 90%, steatohepatitis in 61% and fibrosis (F≥3) in 4% of subjects. AUROC for US, CAP, FLI, HSI, TyG were: 0.90, 0.94, 0.81, 0.74 and 0.75 (p<0.05); regarding liver fibrosis TE, APRI and FIB-4 were 0.95, 0.92 and 0.97 (p<0.05). Two non-invasive-combination models of tests with TyG and FLI or HSI as first tests and US or CAP as second tests had the best diagnosis performance for liver steatosis, AUROC 0.99 (0.97-1 p<0.001), 0.92 (0.77-1 p<0.001). Liver fibrosis model was not performed due to the low proportion of patients with advanced liver fibrosis founded

**Conclusion:** We demonstrated that a combination of TyG with FLI or HSI as first tests and US or CAP as second tests is able to accurately diagnose or exclude the presence of NAFLD, also strongly reducing diagnostic uncertainty area and likelihood of diagnostic errors. This could help avert the need for invasive tests such as liver biopsy.

Table

| Non-invasive Tests | AUC (CI95%)      | p       | Sens % | Spec % | PPV % | NPV % | LH+  | LH-  |
|--------------------|------------------|---------|--------|--------|-------|-------|------|------|
| US                 | 0.90 (0.75-1.00) | 0.002   | 95     | 86     | 98    | 0.67  | 6.66 | 0.06 |
| CAP >238 dB/m      | 0.94 (0.88-1.00) | <0.001  | 88     | 71     | 96    | 0.42  | 3.08 | 0.17 |
| FLI > 41.3         | 0.81 (0.58-1.00) | 0.075   | 88     | 67     | 98    | 0.22  | 2.63 | 0.18 |
| HSI > 41.3         | 0.74 (0.62-0.87) | 0.035   | 60     | 100    | 100   | 0.22  | ∞    | 0.40 |
| TyG > 8.38         | 0.75 (0.49-100)  | 0.032   | 94     | 57     | 95    | 0.50  | 2.18 | 0.11 |
| <b>MODELS</b>      |                  |         |        |        |       |       |      |      |
| 1. TyG/FLI/CAP- US | 0.99 (0.97-1.00) | < 0.001 | 98     | 100    | 100   | 86    | ∞    | 0.02 |
| 2. TyG/HSI/CAP- US | 0.92 (0.77-1.00) | < 0.001 | 98     | 86     | 98    | 86    | 6.89 | 0.02 |

**461 SEX-SPECIFIC INDUCTION OF TRANSCRIPTIONAL RESPONSES TO HCV INFECTION**

**Guido Massaccesi<sup>1</sup>**, Brittany White<sup>1</sup>, Andrea Cox<sup>1</sup>, David L. Thomas<sup>1</sup>, Bryan Bryson<sup>2</sup>, Eileen P. Scully<sup>1</sup>

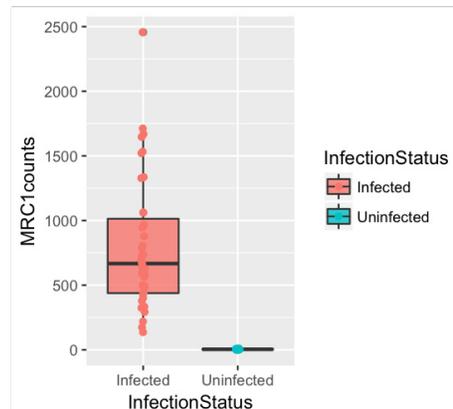
<sup>1</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>Massachusetts Institute of Technology, Cambridge, MA, USA

**Background:** Spontaneous clearance of hepatitis C virus (HCV) infection occurs in ~25% of people. Defining the immunologic determinants of clearance may direct effective vaccination strategies. Female sex is associated with an increased probability of spontaneous HCV clearance (adjusted HR>2 F vs M). We sought to define sex-specific transcriptional features in HCV infection to identify immune responses that may contribute to viral clearance.

**Methods:** Total RNA was extracted from cryopreserved PBMC from a cohort of HIV-negative people with injection drug use: 39 age-matched HCV+(20M, 19F), and 30 HCV- (15M, 15F). Dual index libraries were sequenced (Illumina NovaSeq6000 paired-end, 2x50bp). Analysis of gene counts, multidimensional scaling and gene set enrichment analysis (GSEA) were done in R. Additional analysis was done with a custom gene set derived from RNAseq of in vitro GMCSF-differentiated primary human monocytes. Comparisons of gene expression were done both within and between sex and by HCV infection status.

**Results:** HCV infection status was the primary differentiating factor in gene expression profiles across all of the samples. Excluding sex chromosome encoded genes, HCV infection induced sex-specific regulation of >5000 transcripts in females and >2800 transcripts in males and ~5500 genes shared across the sexes. The top 3 hallmark pathways by GSEA (interferon alpha, interferon gamma and complement) were shared between the sexes, but there were other unique pathways significant at the FDR<0.05 level including negative regulation of TNF alpha signaling by NFKB detected among females but not males. Marked upregulation of MRC1 was noted in the gene count data (HCV+ v HCV- p<2e-16), with the HCV+ females having higher expression of MRC1 (p<5e-6) than males. MRC1 is not included in hallmark pathways but is markedly enriched in an in vitro model of monocyte differentiation with GMCSF conditioning. A custom GMCSF gene set showed ~3-fold enrichment(FDR q<0.05) the gene set in HCV+, with greater enrichment in females.

**Conclusion:** HCV infection markedly alters the immune transcriptome with sex-specific features, such as a marked increase in MRC1 expression, that was reproduced in vitro by stimulating monocytes with GMCSF. These data highlight sex specific features of the innate immune response to HCV; further studies are needed to assess the relationship to HCV clearance.



**462 SARS-CoV-2 REPLICATION IN HEPATOCYTE CELL LINES**

**Kenneth E. Sherman<sup>1</sup>**, Suman Pradhan<sup>1</sup>, Susan D. Rouster<sup>1</sup>, Ling Kong<sup>1</sup>, Heidi Meeds<sup>1</sup>, Jason T. Blackard<sup>1</sup>, Gary E. Dean<sup>1</sup>

<sup>1</sup>University of Cincinnati, Cincinnati, OH, USA

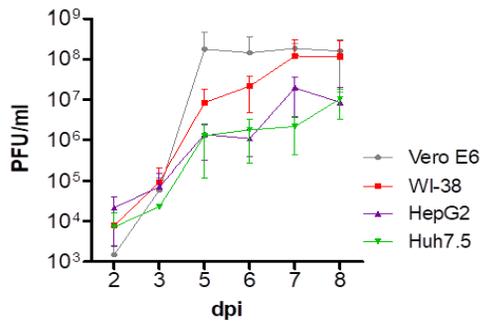
**Background:** A high proportion of patients with COVID-19 demonstrate liver enzyme abnormalities which have been attributed to a variety of etiologies including sepsis, coagulopathy with ischemic injury, and drug effects. We sought to determine the potential for replication and injury due to SARS-CoV-2 infection of hepatocyte cells.

**Methods:** SARS-CoV-2 viral stocks were obtained from ATCC and expanded in Vero E6 cells. The virus was diluted to a multiplicity of infection of 0.1 plaque forming units and placed in medium overlying confluent cells. HepG2 and

Huh7.5 hepatocyte cell lines were utilized, with Vero E6 cells (kidney) and WI-38 (lung) cell cultures serving as infection controls. For each cell line, uninfected cells were also maintained for comparison. Infection experiments were run in triplicate. Plaque assays were used to determine supernatant viral titer on days 2 through 8 post infection. Cell culture morphology was monitored by light microscopy.

**Results:** All cell lines demonstrated significant replication potential with multi-log increase in plaque-forming units by day 3 post-infection. Rapid replication was observed through day 5. This was associated with the presence of severe cell injury with loss of attachment of the monolayer, suggesting that hepatocyte cell death limited overall levels of viral replication.

**Conclusion:** Both HepG2 and Huh7.5 cell lines support active replication of SARS-CoV-2, leading to multi-log increases in viral titer. Replication in these cell lines is accompanied by severe injury leading to loss of attachment and cell death. These findings support the concept that SARS-CoV-2 infection may be associated with liver enzyme abnormalities due to acute viral-induced liver injury.



**Figure:** SARS-CoV-2 virus replication by plaque assay: Cell lines were infected with SARS-CoV-2 virus at a multiplicity of infection (MOI) of 0.1 plaque forming units (PFU)/cell and incubated for 1 hour. Medium was collected and analyzed by plaque assay for viral growth kinetics; days post infection (dpi). Error bars represent standard deviation among triplicate samples.

#### 463 RECENT TRENDS OF HEPATITIS D VIRUS INFECTION AMONG PEOPLE LIVING WITH HIV IN TAIWAN

Shu-Yuan Ho<sup>1</sup>, Li-Hsin Su<sup>1</sup>, Yi-Ching Su<sup>1</sup>, Wen-Chun Liu<sup>1</sup>, Hsin-Yun Sun<sup>1</sup>, Wang-Huei Sheng<sup>1</sup>, Szu-Min Hsieh<sup>1</sup>, Yu-Chung Chuang<sup>1</sup>, Yu-Shan Huang<sup>1</sup>, Sui-Yuan Chang<sup>1</sup>, Chien-Ching Hung<sup>1</sup>

<sup>1</sup>National Taiwan University Hospital, Taipei, Taiwan

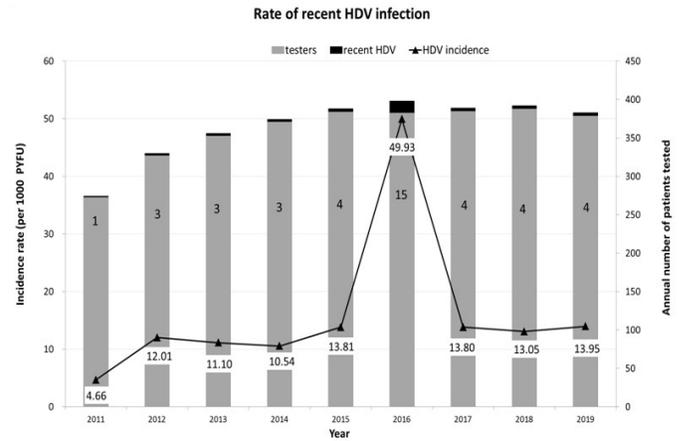
**Background:** People living with HIV (PLWH) who have chronic hepatitis B virus (HBV) infection are at higher risk of hepatitis D virus (HDV) infection. We aimed to investigate the recent trends of incident HDV infection among PLWH who had chronic HBV infection at a university hospital in Taiwan.

**Methods:** Between 2011 and 2018, patients seeking HIV care at the National Taiwan University Hospital were included. HBV serologic markers were determined on entry into care and during follow-up. Sequentially archived blood samples collected from PLWH with chronic HBV infection were retrieved for determinations of anti-HDV antibodies. Blood samples were retrospectively tested for anti-HDV antibodies for those who tested seropositive for HDV during the follow-up. The timing of incident HDV infection was estimated by the midpoint of the last time-point for HDV-seronegative samples and the first time-point for HDV-seropositive samples collected. The study was followed until loss to follow-up, transfer of care, or death of the included PLWH or the end of 2019, whichever occurred first. Incidence rate was estimated for each calendar year.

**Results:** Of 4096 PLWH seeking HIV care during the study period, 505 (12.3%) PLWH who had chronic HBV infection were included after exclusion of those who had no HBV infection at baseline and those without sequential blood samples. Thirty-three (6.5%) PLWH tested seropositive for HDV at baseline. During the follow-up, 41 (8.1%) PLWH, all being male, seroconverted for HDV while on tenofovir-containing combination antiretroviral therapy, with a median age of 43 years (IQR, 35.5–47.7). Of these 41 HDV seroconverters, 36 (87.8%) were men who have sex with men, 2 (4.9%) injection drug users and 2 (4.9%) heterosexuals. Plasma HIV RNA was <20 copies/ml in 61.9% (27/41) and HBV DNA <20 IU/ml in 77.3% (17/22) of the HDV seroconverters. Syphilis was diagnosed in 15.4% of seroconverters, 12.8% tested HCV-seropositive, and 37.1% had persistently elevated aminotransferase levels. The incidence rate increased from 4.66 per 1000 person-years of follow-up (PYFU) in 2011 to 13.81 per 1000 PYFU in 2015. The incidence rate spiked in 2016, with a rate of 49.93

per 1000 PYFU, which fell to 13.80, 13.05, and 13.95 per 1000 PYFU, in 2017, 2018, and 2019, respectively (figure).

**Conclusion:** HDV superinfections continued to occur among PLWH who had chronic HBV infection in the era of tenofovir-containing combination antiretroviral therapy.



#### 464 RETROSPECTIVE STUDY OF HEPATITIS A IMMUNIZATION RATES IN PERSONS WITH HIV

Emily T. Ciocca<sup>1</sup>, Kristen A. Staggars<sup>1</sup>, Jennifer Carey<sup>2</sup>, Antone Opekun<sup>1</sup>, F. B. Hollinger<sup>1</sup>, Wendy A. Keitel<sup>1</sup>, Hana M. El Sahly<sup>1</sup>, Robert L. Atmar<sup>1</sup>, Jennifer Whitaker<sup>1</sup>

<sup>1</sup>Baylor College of Medicine, Houston, TX, USA, <sup>2</sup>Harris Health System, Houston, TX, USA

**Background:** Low HAV vaccination rates in persons with HIV (PWH) and additional risk factors for HAV infection have been described in the US. The objective of this study was to determine HAV vaccination rates among all PWH in the study population and determine associations between vaccination and patient risk factors, demographic, and clinical variables.

**Methods:** A retrospective chart review examined HAV immunization rates in PWH presenting to Thomas Street Health Center and Harris Health Northwest HIV Clinic in Houston, Texas between January 1, 2010 and December 31, 2019. Patients were considered eligible for HAV vaccine if they were HAV IgG negative or never had this test performed and never received prior HAV vaccination. Kaplan-Meier curves summarized time to receiving 1 and 2 doses of HAV vaccine. The cumulative incidence of receiving 1 and 2 doses of HAV vaccine at 6, 12, and 24 months from entry to care was estimated. The log-rank test evaluated associations between subject characteristics and vaccination. Significant factors ( $p < 0.05$ ) were included in a multiple Cox proportional hazards (PH) regression analysis. A reduced Cox PH model was obtained by backwards elimination and forwards re-entering of variables.

**Results:** Of 6,515 patients, 3,074 were eligible for HAV vaccination. At 6 months from entry to care, 6.3% received 1 HAV vaccine dose, followed by 9.6% at 12 months, and 13.7% at 24 months. At 6 months, 1.7% received 2 HAV vaccine doses, followed by 6.0% at 12 months, and 9.8% at 24 months. Over 24 months of follow-up, Hispanic PWH were less likely to receive 1 (HR 0.59; 95% CI: 0.39, 0.90) and 2 HAV vaccine doses (HR 0.51; 95% CI: 0.32, 0.82) after adjusting for men who have sex with men (MSM), and history of chronic hepatitis B and C. MSM (HR 1.48; 95% CI: 1.17, 1.87), those with chronic hepatitis B (HR 3.74; 95% CI: 2.21, 6.35), and chronic hepatitis C (HR 1.88; 95% CI: 1.16, 3.06) were more likely to receive 1 dose of HAV vaccine. Furthermore, patients with chronic hepatitis B (HR 6.60; 95% CI: 3.83, 11.37), chronic hepatitis C (HR 2.71; 95% CI: 1.62, 4.51), and MSM (HR 1.42; 95% CI: 1.07, 1.89) were also more likely to receive 2 doses of HAV vaccine.

**Conclusion:** HAV vaccination rates were low in this study population. Future research to understand the gaps in HAV immunization among our study population, including understanding health disparities that have resulted in decreased vaccination among Hispanic patients, and effective solutions are needed.

Multivariable Cox proportional hazards regression for time to completing 2 HAV vaccinations

|   | Hazards Ratio | 95% C.I.     | p-value        |
|---|---------------|--------------|----------------|
| <b>Race/ Ethnicity</b>                  | Reference     |              | 0.048          |
| Caucasian                               | 0.69          | 0.48 - 1.00  | 0.051          |
| African American                        | 0.51          | 0.32 - 0.82  | <b>0.005</b>   |
| Hispanic                                | 0.75          | 0.18 - 3.13  | 0.697          |
| Other                                   | 1.42          | 1.07 - 1.89  | <b>0.016</b>   |
| <b>Men Who Have Sex with Men</b>        | 6.60          | 3.83 - 11.37 | <b>≤ 0.001</b> |
| <b>History of Chronic HBV infection</b> | 2.71          | 1.62 - 4.51  | <b>≤ 0.001</b> |
| <b>History of Chronic HCV infection</b> |               |              |                |

HAV = hepatitis A virus  
 HBV = hepatitis B virus  
 HCV = hepatitis C virus

**465 HAV REVACCINATION IN SERONEGATIVE OR SEROREVERTED PLWH AFTER PRIMARY VACCINATION**

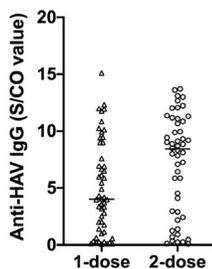
**Guan-Jhou Chen<sup>1</sup>**, Hsin-Yun Sun<sup>1</sup>, Yu-Chung Chuang<sup>1</sup>, Sung-Hsi Huang<sup>1</sup>, Wen-Chun Liu<sup>1</sup>, Yi-Ching Su<sup>1</sup>, Sui-Yuan Chang<sup>1</sup>, Chien-Ching Hung<sup>1</sup>  
<sup>1</sup>National Taiwan University Hospital, Taipei, Taiwan

**Background:** After primary HAV vaccination, people living with HIV (PLWH) have a lower serologic response rate and are more likely to experience loss of seroprotective antibodies during follow-up compared to HIV-negative controls. However, it is not clear as to how HAV revaccination should be administered among PLWH who are non-responders or have lost seroprotective antibodies (seroreverters) after primary vaccination.

**Methods:** In this open-label randomized clinical trial, we enrolled PLWH who tested negative for anti-HAV antibodies ≥4 weeks after completing primary 2-dose HAV vaccination and those who seroreverted after having had seroresponses to primary vaccination. Stratified by the CD4 count, all subjects were randomized at 1:1 ratio to receive either 1 or 2 doses (4 weeks apart) of HAV vaccine with a block size of 4. At week 4, week 8 (only in 2-dose group), week 24, and week 48 after HAV revaccination, the levels of anti-HAV IgG were determined with the use of a semiquantitative chemiluminescence immunoassay (ARCHITECT HAVAb-IgG, Abbott, Germany). We report the interim analysis of the results at week 24.

**Results:** A hundred and two participants, 50 in the 2-dose and 52 in the 1-dose group, had completed follow-up at week 24. All participants were male (mean age, 38.6 years), with median CD4 of 461 cells/mm<sup>3</sup>, and plasma HIV RNA <20 copies/ml in 90.2% before revaccination. The baseline characteristics were balanced between the two groups. The serologic responses at week 24 was similar 84.0% for the 2-dose revaccination group and 78.8% for the 1-dose group (difference, 5.2%; 95% CI, -9.9%-20.2%). However, participants in the 2-dose group had a significantly higher anti-HAV IgG level, indicated by the S/CO value (median, 8.4 vs. 4.0), compared to those in 1-dose group (Figure). All of PLWH in the two groups (22 in 2-dose and 24 1-dose group) who were seroreverters after primary vaccination mounted good serologic response. Among PLWH who failed to mount seroresponse after primary vaccination, 71.4% (20/28) and 60.7% (17/28) of the participants responded to 2-dose and 1-dose HAV revaccination, respectively (difference, 10.7%; 95% CI, -13.9%-35.4%).

**Conclusion:** Among PLWH who had no responses to primary 2-dose HAV vaccination or those whose anti-HAV antibodies had waned, revaccination with 1 or 2 doses of HAV vaccine resulted in similar serologic responses. PLWH who received 2 doses of HAV vaccine had higher anti-HAV IgG level than those who received 1 dose of vaccine.



**466 LOW RATE OF VACCINATION AND RISK OF INCIDENT HEPATITIS A AMONG HIV-INFECTED MSM**

**Marta Fernandez-Fuertes<sup>1</sup>**, Anaïs Corra-Gomez<sup>1</sup>, Pilar Rincon<sup>1</sup>, Ana Fuentes<sup>2</sup>, Esther Serrano<sup>2</sup>, Alejandro Gonzalez-Serna<sup>1</sup>, Federico Garcia<sup>2</sup>, Luis M Real<sup>1</sup>, Juan A. Pineda<sup>1</sup>, Juan Macías<sup>1</sup>

<sup>1</sup>Hospital Universitario de Valme, Seville, Spain, <sup>2</sup>Hospital Universitario San Cecilio, Granada, Spain

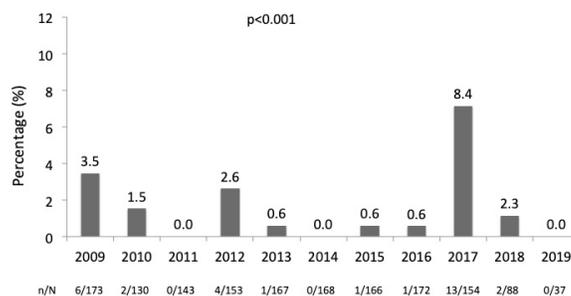
**Background:** Periodic outbreaks of hepatitis A virus (HAV) infection in men who have sex with men (MSM) have been observed in Western countries. Low vaccination uptake in HIV-infected individuals could drive newer outbreaks of HAV. Because of this, we aimed at evaluating the incidence of and the risk factors for HAV infection in HIV-infected patients. We also assessed the rates of HAV vaccination among this population.

**Methods:** In this retrospective cohort study all HIV-infected patients followed at our Unit from January 2008 to December 2019 were analyzed. Patients were included if they had at least two frozen samples available collected at least 12 months apart. HAV incident cases were defined as individuals with a baseline negative and an end of follow-up positive test for serum HAV antibodies. The year of seroconversion was investigated by testing sera stored yearly.

**Results:** Overall, 915 patients were included, 272 (29.7%) of them were HAV IgG seronegative at baseline. Twenty-seven (9.9%) susceptible individuals became infected during the study period. Among patients with HAV incident infection, 16 (59.3%) were MSM and 11 (40.7%) were non-MSM individuals (p=0.181). Incident cases peaked in 2009, 2012 and 2017 (Figure). Multivariate analysis, adjusted by age, sex, risk group and CDC stage, showed an independent association between incident HAV infection and MSM [adjusted odds ratio (95% confidence ratio): 4.71 (1.49 – 14.83), p=0.008]. Among patients HAV IgG seronegative at baseline, 104 (38%) were vaccinated against HAV along the study period. Ten (9.6%) individuals did not show detectable anti-HAV antibodies after vaccination, and one patient (1%) lost immunity against HAV after 4 years of vaccination. Four (3.8%) non-responders to vaccination showed anti-HAV seroconversion after 5 to 12 years since vaccination.

**Conclusion:** The incidence of HAV infection among HIV-infected population in our area remains low and stable, with periodical outbreaks involving mainly non-immunized MSM. A significant proportion of HIV-infected patients remain susceptible to HAV infection due to insufficient vaccine uptake and limited response to vaccination. Importantly, patients not responding to HAV vaccination are at risk of infection.

Figure. Annual HAV incidence in susceptible patients



**467 SUCCESSFUL PERITRANSPLANT SOFOSBUVIR-BASED DAA THERAPY IN HIV/HCV-COINFECTED SUBJECTS**

**Dominic Amara<sup>1</sup>**, Marion Peters<sup>1</sup>, Shyam Kottitil<sup>2</sup>, Norah Terrault<sup>3</sup>, Jennifer Husson<sup>2</sup>, Shirish Huprikar<sup>4</sup>, Mark S. Sulkowski<sup>5</sup>, Christine Durand<sup>5</sup>, Rodney Rogers<sup>1</sup>, Joshua Grab<sup>1</sup>, Henry Masur<sup>6</sup>, Peter Stock<sup>1</sup>, for the STOP-CO Investigators

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>University of Maryland, Baltimore, MD, USA, <sup>3</sup>University of Southern California, Los Angeles, CA, USA, <sup>4</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>5</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>6</sup>National Institutes of Health, Bethesda, MD, USA

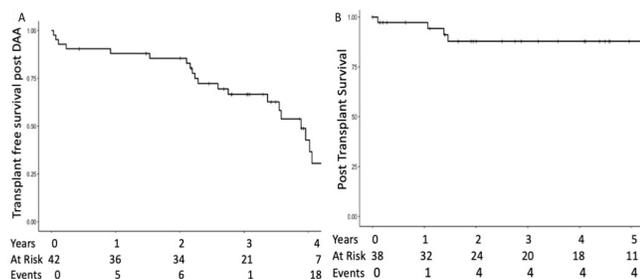
**Background:** Direct acting antiviral (DAA) therapy has transformed the management of human Immunodeficiency virus (HIV) and hepatitis C (HCV) coinfecting patients with advanced liver disease. STOP-Coinfection was a multi-center, prospective and retrospective, open-label study using sofosbuvir-based DAA therapy to treat HIV/HCV coinfecting participants pre- or post-liver transplant (LT).

**Methods:** The study included adults living with HIV and chronic HCV and end-stage liver disease pre-LT and any stage of liver disease post-LT; HCV genotypes 1, 4, 5 or 6 with pre-treatment serum HCV RNA  $\geq 1000$  IU/mL. Pre-LT participants had a baseline Child's Pugh Turcotte (CPT) score  $\geq 7$  and Model for End-Stage Liver Disease (MELD)  $\geq 6$  to  $\leq 30$ . Endpoints were proportion of participants achieving sustained virologic response (SVR) and reversal in decompensation.

**Results:** 68 participants with end stage liver disease were enrolled, 26 had hepatocellular carcinoma. 42 participants were treated pre-LT and 26 post-LT. 93% achieved SVR and DAA therapy was well tolerated. All participants completed therapy without dose reduction or transfusion; 8 required  $\geq 2$  courses of therapy. All participants had controlled HIV on ART with stable CD4 counts and occasional low detectable HIV viral load. 28 participants experienced 41 serious adverse events during treatment. Despite HCV cure, 12 end-stage liver disease participants required subsequent LT, 7 for decompensated liver disease. In 33 of the 42 participants treated pre-LT, MELD was available pre and post DAA treatment and pre-LT. Among the 19 participants with pretreatment MELD  $< 15$ , 53% had improvement in MELD (-1 to -6); 37% had worsening of MELD (2-15); 10% no change; and 26% had post DAA treatment MELD  $\geq 15$ . Among those 14 participants with pretreatment MELD  $\geq 15$ , 64% had improvement in MELD (-1 to -30); 29% had worsening of MELD (2 to 21); 7% no change; and 43% had MELD  $< 15$ . 13 participants died, 10 with decompensated liver disease pre-LT and 3 post-LT. Overall, transplant free survival was 42.8% at 4 years (figure A) and post-LT survival was 87.9% at 5 years (figure B).

**Conclusion:** We conclude that sofosbuvir-based DAA therapy is safe and highly effective in HCV-HIV patients with decompensated liver disease and post-LT, with post-LT survival rates comparable to other indications. This removes one of the last barriers to LT in this challenging cohort of recipients and likely will increase LT-free survival.

Figure Kaplan Meier Survival Curves of those participants who were treated pre-LT (A: transplant free survival) and those who received liver transplant (B: post-transplant survival). Included are the number of participants at risk and cumulative number of events (death and transplant) over years post DAA therapy (A) and post-transplant (B).



#### 468 PREDICTION MODEL FOR END-STAGE LIVER DISEASE AMONG PEOPLE WITH HIV IN THE NA-ACCORD

**H. Nina Kim**<sup>1</sup>, Robin M. Nance<sup>1</sup>, Heidi Crane<sup>1</sup>, Bridget M. Whitney<sup>1</sup>, Keri N. Althoff<sup>2</sup>, Richard Moore<sup>3</sup>, Michael J. Silverberg<sup>4</sup>, Angel Mayor<sup>5</sup>, Edward R. Cacyay<sup>6</sup>, Mark Hull<sup>7</sup>, Vincent Lo Re<sup>8</sup>, Marina B. Klein<sup>9</sup>, Joseph A. Delaney<sup>10</sup>, Mari M. Kitahata<sup>1</sup>, for the North American AIDS Cohort Collaboration on Research and Design of IeDEA

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>3</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>4</sup>Kaiser Permanente, Oakland, CA, USA, <sup>5</sup>Universidad Central del Caribe, Bayamon, Puerto Rico, <sup>6</sup>University of California San Diego, San Diego, CA, USA, <sup>7</sup>University of British Columbia, Vancouver, Canada, <sup>8</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>9</sup>McGill University, Montreal, Canada, <sup>10</sup>University of Manitoba, Winnipeg, Canada

**Background:** End-stage liver disease (ESLD) is a leading cause of non-AIDS death among people living with HIV (PWH). No predictive tool for hepatic decompensation currently exists in PWH. We sought to develop a risk prediction model for ESLD in a multicenter consortium of HIV cohorts with rigorously adjudicated clinical outcomes.

**Methods:** PWH who received care from one of 12 US and Canadian cohorts of the North American AIDS Cohort Collaboration on Research and Design from 2000-2016 and had FIB-4  $> 1.45$  were included. First occurrence of ascites, variceal bleed, spontaneous bacterial peritonitis or hepatic encephalopathy was verified by standardized medical record review. Those with prevalent ESLD

(present from cohort entry to 180 days after) were excluded. A subset of cohorts were randomly selected until ~20% of events were achieved and set aside for testing; remainder was used for derivation. Bayesian model averaging was used to select predictors among liver and HIV biomarkers and key clinical diagnoses (HBV, HCV, diabetes and alcohol abuse/dependence). Variables with  $> 50\%$  probability of being in the best fitting model were included, along with age and sex. Harrell's C statistic was used to assess model discrimination.

**Results:** Of 40,106 PWH, 13,787 (34%) had FIB-4  $> 1.45$ . Among these (82% male; 54% black; mean age 48 years), 390 ESLD events were identified over a mean 5.4 years. Of ESLD cases, 52% had hepatitis C, 15% hepatitis B and 31% had a history of alcohol. Twelve factors (Table) together predicted ESLD risk moderately well (C-statistic 0.78, 95% CI 0.76, 0.81). The model included age, sex, race/ethnicity and routinely collected laboratory values reflecting hepatic impairment (serum albumin, AST, total bilirubin, platelets) and lipid metabolism (triglycerides, HDL, total cholesterol). Chronic HBV and HCV were among these. Neither CD4 cell count nor HIV viral level (log-transformed) had  $> 10\%$  probability of being included in the best fitting predictive model for ESLD, however their predictive contribution was likely mediated through other selected variables. The testing subset comprised 3,173 PWH across 3 cohorts (90% male; 14% black; mean age 49 years) and yielded 112 ESLD events over a mean of 4.3 years follow-up. Our model performed well in this testing set (C-statistic 0.81, 95% CI 0.76, 0.86).

**Conclusion:** This model developed specifically for PWH includes readily accessible clinical parameters, appears to work well in a diverse population and may provide a convenient tool for ESLD prediction.

**Table.** Prediction model for end-stage liver disease including covariates with probability  $> 50\%$  of being in best-fitting model by Bayesian model averaging, along with age and sex

| Covariate                     | HR    | 95% CI |       | P-value   |
|-------------------------------|-------|--------|-------|-----------|
| Age                           | 1.014 | 1.001  | 1.027 | 0.033     |
| Female                        | 0.775 | 0.578  | 1.039 | 0.088     |
| Race/ethnicity (ref: White)   |       |        |       |           |
| Black                         | 0.564 | 0.451  | 0.706 | $< 0.001$ |
| Hispanic                      | 1.390 | 0.871  | 2.216 | 0.167     |
| Other                         | 0.464 | 0.245  | 0.880 | 0.019     |
| Albumin, g/dl (per doubling)  | 0.091 | 0.058  | 0.144 | $< 0.001$ |
| AST, U/L                      | 1.001 | 1.001  | 1.002 | $< 0.001$ |
| Total bilirubin, mg/dl        | 1.173 | 1.098  | 1.252 | $< 0.001$ |
| Platelets, $10^3/\mu\text{l}$ | 0.992 | 0.990  | 0.993 | $< 0.001$ |
| Triglycerides, mg/dl          | 1.001 | 1.001  | 1.002 | $< 0.001$ |
| HDL, mg/dl                    | 1.015 | 1.007  | 1.023 | $< 0.001$ |
| Total cholesterol, mg/dl      | 0.993 | 0.989  | 0.997 | 0.002     |
| Chronic hepatitis B           | 1.964 | 1.468  | 2.627 | $< 0.001$ |
| Chronic hepatitis C           | 2.354 | 1.908  | 2.904 | $< 0.001$ |

HR, hazard ratio (per unit change in laboratory value unless otherwise indicated); CI, confidence interval; ref, reference; AST, aspartate aminotransferase; HDL, high-density lipoprotein.

#### 469 LIVER STIFFNESS-BASED STRATEGIES FOR VARICEAL BLEEDING PREDICTION AFTER HCV CURE

**Anaïs Corma-Gomez**<sup>1</sup>, Juan Macías<sup>1</sup>, Luis Morano<sup>2</sup>, Antonio Rivero<sup>3</sup>, Francisco Tellez<sup>4</sup>, Maria José Ríos<sup>5</sup>, Marta Santos<sup>6</sup>, Miriam Serrano<sup>7</sup>, Rosario Palacios<sup>8</sup>, Dolores Merino<sup>9</sup>, Luis M Real<sup>10</sup>, Ignacio De Los Santos<sup>11</sup>, Francisco J. Vera-Méndez<sup>12</sup>, Juan A. Pineda<sup>1</sup>, for RIS-HEP and the GEHEP 011 Study Groups

<sup>1</sup>Hospital Universitario de Valme, Seville, Spain, <sup>2</sup>Complejo Hospitalario Universitario de Vigo, Vigo, Spain, <sup>3</sup>Hospital Universitario Reina Sofia, Cordoba, Spain, <sup>4</sup>Hospital Universitario de Puerto Real, Cadiz, Spain, <sup>5</sup>Hospital Universitario Virgen Macarena, Sevilla, Spain, <sup>6</sup>Hospital Universitario de Jerez, Jerez de la Frontera, Spain, <sup>7</sup>Hospital Universitario de Gran Canaria Doctor Negrin, Las Palmas de Gran Canaria, Spain, <sup>8</sup>Hospital Universitario Virgen de la Victoria, Malaga, Spain, <sup>9</sup>Hospital Universitario Juan Ramón Jiménez, Huelva, Spain, <sup>10</sup>Hospital Universitario de Valme, Seville, Spain, <sup>11</sup>Hospital Universitario de La Princesa, Madrid, Spain, <sup>12</sup>Hospital General Universitario Santa Lucía, Cartagena, Spain

**Background:** Liver stiffness (LS)-based strategies identify patients with low risk of developing esophageal variceal bleeding (VB) episodes, in whom unnecessary upper esophagogastroduodenoscopy (UGE) screening can be safely avoided, in the setting of HCV active infection. However, data on the accuracy of the criteria predicting this outcome in HCV-infected patients with cirrhosis, with or without HIV-coinfection, after sustained virological response (SVR), are scarce.

**Methods:** Multicenter prospective cohort study, where HCV-monoinfected patients and HIV/HCV-coinfected individuals were included if: 1) SVR with DAA-based therapy; 2) LS  $\geq 9.5$  kPa previous to treatment; 3) LS measurement at the SVR time-point  $\geq 14$  kPa. Diagnostic accuracy of HEPAVIR (favorable status LS < 21 kPa), expanded Baveno VI (favorable status LS 110000/mm<sub>3</sub>) and HIV cirrhosis criteria (favorable status LS 110000/mm<sub>3</sub>), at the time of SVR, was evaluated. Missed VB episodes, negative predictive values (NPV), and number of spared UGEs were specifically assessed. Sensitivity analyses by HIV-coinfection were performed.

**Results:** 441 patients were included, 286 (65%) coinfecting with HIV. 11 (2.5%) individuals developed a VB episode after SVR. 3 (0.7%) of them, had experienced a VB episode before SVR. The incidence rate of this event in patients with no VB prior to SVR was 0.5 (95% CI 0.3-1.0) x100 person-years. In patients without a previous VB episode, HEPAVIR, expanded Baveno VI and HIV cirrhosis criteria achieved NPV for first VB episode after SVR of 99.5% (97.2%-100%), 100% (97.8%-100%) and 100% (98.1%-100%) while sparing 45%, 39% and 44% of UGEs, respectively. When considering HIV-coinfection, the performance of the three criteria was similar; in HCV-monoinfected, HEPAVIR, expanded Baveno VI and HIV cirrhosis criteria missed no bleeding events, maintaining NPV at 100% and sparing 55%, 39% and 44% of UGEs, respectively. Among HIV/HCV-coinfected individuals, NPV for this event was 99.2% (95.4%-100%), 100% (96.5%-100%) and 100% (96.9%-100%) for HEPAVIR, expanded Baveno VI and HIV cirrhosis criteria, respectively. In this subset the employment of these criteria allowed to spare 44%, 38% and 43% of UGEs, correspondingly.

**Conclusion:** After SVR, LS-based strategies identify HCV-infected patients, with or without HIV-coinfection, with low risk of developing VB. HIV cirrhosis criteria perform the best, sparing a higher number of UGEs without missing bleeding episodes.

**470 MODULATION OF GUT FLORA PROMOTES THE REGRESSION OF ANAL DYSPLASIA IN HIV+ MSM**

**Eugenio Nelson Cavallari<sup>1</sup>, Letizia Santinelli<sup>1</sup>, Gabriella De Girolamo<sup>1</sup>, Giuseppe P. Innocenti<sup>1</sup>, Claudia Pinacchio<sup>1</sup>, Luigi Celani<sup>1</sup>, Marco Ridolfi<sup>1</sup>, Alessandro Russo<sup>1</sup>, Giancarlo Ceccarelli<sup>1</sup>, Mary A. Venneri<sup>1</sup>, Antonio Ciardi<sup>1</sup>, Carolina Scagnolari<sup>1</sup>, Alessandra Pierangeli<sup>1</sup>, Claudio M. Mastroianni<sup>1</sup>, Gabriella D'Ettoire<sup>1</sup>**  
<sup>1</sup>Sapienza University of Rome, Rome, Italy

**Background:** Anal microbiota of HIV+ MSM is rich in Prevotella and Bacteroides, genus that are observed in women with bacterial vaginosis (BV). BV increases genital HPV infection and persistence leading to the development of dysplasia. Degradation of mucus layer, increase of pH, alteration of several cellular pathways and impairment of T cell response are some of the mechanisms underlying the ease of HPV infection during BV. Lactic acid bacilli showed protective properties against HPV infection in women, through the restoration of epithelial lining, reduction of local pH and promotion of cytotoxic activity against HPV infected cells. Oral administration of lactic bacilli promotes HPV clearance and regression of dysplasia in women's genital tract. Here we report the preliminary results of an ongoing quadruple blind, randomized, placebo controlled clinical study on the use of oral bacteriotherapy in HIV+ MSM with anal HPV infection (ClinicalTrials.gov Identifier: NCT04099433).

**Methods:** 20 HIV+ MSM concluded the study to date. At baseline (T0), participants underwent anal HPV test, anal cytology and histology of high resolution anoscopy (HRA) driven biopsies. Participants were randomly assigned to a mixture of probiotics (1800 billion bacteria/day) or placebo, for 6 months. At the end of the study (T6) the same operator repeated the investigations performed at T0. Pathology, virology and statistical analysis were conducted blindly.

**Results:** Main characteristics of the study population and univariate outcomes are reported in Table 1. Clearance of HPV infection was defined as negative HPV swab at T6 or evidence of a different genotype in respect to T0. In the overall population, at T6 only 3 participants in the treatment arm showed negative HPV swab (p=0.039). Impression of overall improvement or worsening were blindly assessed for each participant by HRA provider at the end of the second HRA, after reviewing images from T0. The multivariate logistic regression analysis showed that exposure to bacteriotherapy increased clearance of HPV (OR 8.9, 95% CI: 1.2-71, p=0.028), increased clearance of SIL (OR 80.0, 95% CI: 4.3-1488, p<0.001), decreased persistence and worsening of SIL (OR 0.047, 95% CI: 0.004-0.552, p=0.009) as well as the onset of new SIL (OR 0.107, 95% CI: 0.014-0.84, p=0.025).

**Conclusion:** Although individuals randomized in the treatment arm were younger than those exposed to placebo, administration of oral bacteriotherapy significantly improved clearance of anal HPV infection and anal SIL.

|  | PLACEBO         | BACTERIOTHERAPY | p-value |
|--|-----------------|-----------------|---------|
| Participants                                       | 11              | 9               | na      |
| Anal receptive intercourse                         | 11 (100%)       | 9 (100%)        | 1.000   |
| Age  | 55 (50.5-57.5)  | 44 (36-46)      | 0.005   |
| Cigarettes smokers                                 | 6 (55%)         | 3 (33%)         | 0.367   |
| Diabetes   | 1 (9%)          | 0               | 0.341   |
| Years of HIV infection                             | 18 (10.5-25.5)  | 12 (10-14)      | 0.081   |
| Received HPV vaccination                           | 0               | 0               | 1.000   |
| CD4 nadir (cells/ $\mu$ L)                         | 262 (113-406)   | 460 (350-532)   | 0.387   |
| CD4 T0 (cells/ $\mu$ L)                            | 700 (540-897)   | 877 (700-936)   | 0.606   |
| CD4 T6 (cells/ $\mu$ L)                            | 703 (477-940)   | 943 (794-994)   | 0.185   |
| $\Delta$ CD4 (T1-T0) (cells/ $\mu$ L)              | -17 (-1004-242) | -13 (-472-243)  | 0.766   |
| NRTI   | 9 (82%)         | 8 (89%)         | 0.673   |
| INSTI  | 8 (73%)         | 4 (44%)         | 0.227   |
| NNRTI  | 3 (27%)         | 5 (56%)         | 0.227   |
| PI   | 2 (18%)         | 1 (11%)         | 0.673   |
| Partners during the study                          | 2 (1-4)         | 3 (1-5)         | 0.738   |
| Partners during lifetime                           | 50 (40-250)     | 100 (100-150)   | 0.341   |
| high risk HPV T0                                   | 5 (45%)         | 6 (67%)         | 0.367   |
| high risk HPV T6                                   | 6 (55%)         | 3 (33%)         | 0.367   |
| HPV clearance T6                                   | 2 (18%)         | 6 (67%)         | 0.001   |
| Number of SIL T0 (histology)                       | 1 (1-2)         | 2 (1-3)         | 0.714   |
| Number of SIL T6 (histology)                       | 2 (2-4)         | 1 (0-1)         | 0.053   |
| Participants with HSIL                             | 0               | 2 (22%)         | 0.395   |
| Individuals with persistent worsen SIL at T6 (HRA) | 7 (78%)         | 1 (11%)         | 0.004   |
| Individuals with new onset of SIL at T6 (HRA)      | 8 (73%)         | 2 (22%)         | 0.023   |
| Individuals with regression of SIL at T6 (HRA)     | 1 (9%)          | 6 (67%)         | 0.001   |
| Impression of overall improvement (HRA)            | 9 (82%)         | 2 (22%)         | <0.001  |
| Impression of overall worsening (HRA)              | 0               | 7 (78%)         | <0.001  |

Table 1. Characteristics of the study groups and univariate analysis results expressed as median (IQR 25-75) or absolute frequencies (relative frequencies). SIL: squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion.

**471 RISK OF AND RISK FACTORS FOR COLORECTAL CANCER IN MALE VETERANS WITH CONTROLLED HIV**

**Elizabeth Chiao<sup>1</sup>, Jennifer R. Kramer<sup>1</sup>, Yongquan DONG<sup>1</sup>, Christine M. Hartman<sup>1</sup>, Kathryn Royle<sup>1</sup>, Peter Richardson<sup>1</sup>, Suchismita Raychaudhury<sup>1</sup>, Sarah Ahmed<sup>1</sup>, Donna L. White<sup>1</sup>, Aaron P. Thrift<sup>1</sup>**  
<sup>1</sup>Baylor College of Medicine, Houston, TX, USA

**Background:** Non AIDS Defining Cancers (NADCs) are an increasing public health problem for the growing population of PWH in the U.S. As PWH age, cancers associated with aging including Colorectal Cancer (CRC) will increase. We conducted this study to determine the incidence of and risk factors for CRC among Veterans living with HIV.

**Methods:** This is retrospective cohort study among HIV-positive male veterans. We included Veterans aged  $\geq 18$  years living with HIV using an algorithm including ICD-9 codes, laboratory and pharmacy data from CDW. Colorectal Cancers were identified using the ICD-0 codes from the VA cancer registry and identifying additional cases through ICD-9/10 code searches for colon and rectal cancer codes in the CDW. Follow-up time at risk was calculated from their date of HIV diagnosis to the development of CRC, death, or 12/31/2016, whichever was earlier. We examined incidence per 100,000 PY and Cox proportional hazards regression models to determine risk factors for disease.

**Results:** We included 44,160 HIV-positive male patients in the primary analysis, of whom 25,088 (56.8%) were considered to have had well-controlled HIV disease. The mean age of the HIV-positive cohort was 47.3 years (standard deviation, 10.7); and was similar for the sub-cohort of patients with well-controlled HIV disease (47.9 years). The majority of the HIV-positive patients were Black (52.3%) and had a history of tobacco smoking (75.7%), and approximately half were overweight or obese at their HIV index date. The mean duration of follow-up following HIV index date from the CDW was 8.96 years (standard deviation, 5.65) for all HIV-positive patients, and 9.88 years (standard deviation, 5.48). Among the well-controlled cohort, we found that older age and nadir CD4  $\leq 200$  remained independently associated with increased risk for CRC, while the inverse association with statin use was somewhat stronger and statistically significant (HR, 0.60; 95% CI, 0.36-1.00). Among patients with well-controlled HIV infection, diabetes was also associated with higher risk for CRC (HR, 1.57; 95% CI, 1.00-2.48). (See Table 1)

**Conclusion:** In this cohort study of Veterans with well-controlled HIV, in addition to older age, and diabetes, we found that lower Nadir CD4 count was associated with increased risk for Colorectal Cancer. In addition, we found that statin utilization decreased the risk for colorectal cancer in this cohort. Further

research is needed to understand the role of immunosuppression in Colorectal Cancer Risk among PWH.

**Table 1:** Risk factors for colorectal cancer among veterans with well-controlled\* HIV infection (N=25,088)

| Factors                      | CRC (n=105)       | Colon (n=84)      | Rectum (n=22)     |
|------------------------------|-------------------|-------------------|-------------------|
|                              | HR (95% CI)       | HR (95% CI)       | HR (95% CI)       |
| <b>Age at HIV diagnosis</b>  |                   |                   |                   |
| <40                          | 1.00 (Ref)        | 1.00 (Ref)        | 1.00 (Ref)        |
| 40-49                        | 2.83 (1.08, 7.41) | 3.13 (0.91, 10.8) | 2.41 (0.52, 11.3) |
| 50-64                        | 7.66 (3.05, 19.2) | 11.6 (3.60, 37.5) | 2.01 (0.40, 10.1) |
| ≥65                          | 17.9 (6.40, 50.0) | 18.5 (5.01, 68.3) | 19.2 (3.58, 103)  |
| <b>Race/Ethnicity</b>        |                   |                   |                   |
| White                        | 1.00 (Ref)        | 1.00 (Ref)        | 1.00 (Ref)        |
| Black                        | 1.02 (0.87, 1.56) | 1.33 (0.83, 2.15) | 0.35 (0.13, 0.94) |
| Other/Unknown                | 1.44 (0.77, 2.69) | 1.73 (0.87, 3.47) | 0.70 (0.16, 3.08) |
| <b>Alcohol, ever</b>         | 1.05 (0.69, 1.61) | 1.09 (0.68, 1.76) | 0.87 (0.34, 2.21) |
| <b>Smoking, ever</b>         | 1.08 (0.66, 1.76) | 0.82 (0.49, 1.37) | 3.27 (0.75, 14.3) |
| <b>Baseline BMI</b>          |                   |                   |                   |
| <25                          | 1.00 (Ref)        | 1.00 (Ref)        | 1.00 (Ref)        |
| 25-30                        | 1.02 (0.66, 1.57) | 0.96 (0.60, 1.54) | 1.30 (0.43, 3.91) |
| ≥30                          | 0.96 (0.52, 1.77) | 0.66 (0.31, 1.38) | 3.85 (1.25, 11.9) |
| <b>Year of HIV diagnosed</b> |                   |                   |                   |
| 1985-1995                    | 1.00 (Ref)        | 1.00 (Ref)        | 1.00 (Ref)        |
| 1996-2005                    | 1.06 (0.66, 1.69) | 1.11 (0.65, 1.90) | 0.75 (0.29, 1.91) |
| 2006-2016                    | 0.76 (0.39, 1.46) | 0.78 (0.38, 1.61) | 0.47 (0.09, 2.51) |
| <b>Nadir CD4</b>             |                   |                   |                   |
| >200                         | 1.00 (Ref)        | 1.00 (Ref)        | 1.00 (Ref)        |
| ≤200                         | 1.75 (1.17, 2.61) | 1.62 (1.03, 2.54) | 2.47 (1.02, 5.95) |
| <b>Statin, ever</b>          | 0.60 (0.36, 1.00) | 0.66 (0.37, 1.16) | 0.52 (0.17, 1.59) |
| <b>Diabetes, yes</b>         | 1.57 (1.00, 2.48) | 1.76 (1.07, 2.91) | 1.09 (0.38, 3.11) |

\*Veterans with well-controlled HIV disease as those on ART therapy (≥ 2 classes) that had achieved viral suppression status for at least 60% of total follow-up time.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

#### 472 LACK OF TLRs ACTIVATION IN ANAL CELLS OF HIV+ MEN MAY CONTRIBUTE TO HPV PERSISTENCE

Letizia Santinelli<sup>1</sup>, Mirko Scordio<sup>1</sup>, Federica Frasca<sup>1</sup>, Claudia Pinacchio<sup>1</sup>, Gabriella D'Ettore<sup>1</sup>, Eugenio Nelson Cavallari<sup>1</sup>, Leonardo Sorrentino<sup>1</sup>, Paolo Gozzo<sup>1</sup>, Alessandra Pierangeli<sup>1</sup>, Carolina Scagnolari<sup>1</sup>

<sup>1</sup>Sapienza University of Rome, Rome, Italy

**Background:** Persistent infection with high-risk (HR) HPVs is associated with anal cancer, with a particularly high risk in HIV+ individuals. Dampened innate immunity in the cervical mucosa is a mechanism by which HR HPVs interfere with innate immune responses, contributing to viral persistence. No such studies were conducted in HPV infected anal cells; hence, we aimed to investigate Toll Like Receptors (TLR) expression to clarify the process that leads to HPV persistence in HIV+ patients.

**Methods:** Anal canal brushing samples were prospectively collected from patients attending a proctology clinic. Anal cells were divided into two aliquots: one for nucleic acid extraction and one for anal cytology. Detection of HPV DNA and genotyping were performed by PCR and sequencing To characterize the expression levels of TLRs in the mucosa of HPV-infected compared with HPV-uninfected HIV+ men, we quantified transcripts of TLR2, TLR3, TLR4, TLR8, TLR9 and, as marker of IFN response, ISG15 and ISG56. A subgroup of patients underwent anal brushing after one year in follow-up visits, in order to evaluate persistence of HPV infection.

**Results:** 86 Caucasian HIV-infected men (median age 46 ±11 years), on long-term ART, were enrolled in this study. HPV DNA was detected in 83.7% of anal samples, with 37/72 (51.4%) being HR-HPVs. The most common genotypes were HPV 6 (26.4%) and HPV 16 (11.1%). More than half patients (57.5%) had LSIL or higher in anal cytology. Overall, HPV-infected patients expressed decreased levels of TLRs, with respect to the HPV-negative. ISG15 expression also was significantly lower in the HPV-positive with respect to the negative, whereas ISG56 did not differ. In the follow-up anal brushings, 31% (9/29) of those HPV positive at the first study visit, cleared spontaneously the infection. Of those still HPV positive, 11/20 (55%) had the same genotype and 9/20 (45%) were infected with a different HPV. Interestingly, those who cleared HPV infection in the follow-up brushing, had significantly higher expression of all TLRs at baseline, with respect to those persistently infected.

**Conclusion:** In the anal mucosa of HIV+ men, HPV seemed to poorly activate the expression of most TLRs, unlike what was reported in the cervical mucosa. Further studies in anal cells of patients in the early stages of infection and at follow-up, including HIV-negative patients, could help to clarify changes in the

innate antiviral immune responses that are likely to favor HPV persistence and anal cancer.

#### 473 ANAL HPV CONCORDANCE AND PERSISTENCE: ROLE IN ANAL TUMORS IN WOMEN LIVING WITH HIV

Kevin Weiss<sup>1</sup>, Tinaye Mutetwa<sup>1</sup>, Courtney Chan<sup>1</sup>, Yuxin Liu<sup>1</sup>, Michael M. Gaisa<sup>1</sup>, Keith Sigel<sup>1</sup>

<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA

**Background:** Women living with HIV (WLH) are highly susceptible to high-risk human papillomavirus (HPV)-associated precancer and cancer in the lower anogenital tract. The dynamics of anal and cervical HPV infection and their relationship to anal cancer precursors are not well studied. We aimed to determine the prevalence of anal and/or cervical HPV infection among WLH as well as their association with anal cancer precursors, i.e. high-grade squamous intraepithelial lesions (HSILs).

**Methods:** The current study included 144 WLH who underwent anal cancer screening at our program between 2012-19 and met the following criteria: (1) anal HPV DNA testing (HPV16, 18 and 12 other high-risk types) upon initial and follow-up visits; (2) cervical HPV DNA testing within six months of the initial visit; and (3) high-resolution anoscopy (HRA) examination and biopsy within 3 months of anal HPV testing. We analyzed anal and cervical HPV coinfection and concordance, anal HPV persistence/clearance, and the incidence of anal HSIL by anal/cervical HPV status.

**Results:** At baseline, 45% of the cohort had anal high-risk HPV (hrHPV) infection alone, 3% had cervical hrHPV infection alone, while 28% had anal/cervical coinfection. Biopsy-proven HSIL was detected in 31%. Among subjects with coinfection, 56% had concordance of HPV types at both genital sites. Among WLH with anal HPV at baseline, HPV was persistent in 54% of subjects and cleared in 46% upon follow-up (median interval: 534 days). The rate of anal HPV persistence was similar between subjects with anal infection alone and those with anal/cervical coinfection. Anal HSIL was associated with persistent anal HPV infection, anal HPV type 16/18, but not with cervical HPV type 16/18 infection (incidence rate ratios 6.8 (p<0.01), 6.2 (p<0.001), and 1.4 (p = 0.44), respectively).

**Conclusion:** In WLH, anal HPV infection may be more common than cervical infection. Persistent anal HPV infection appears to be independent of cervical HPV status. Our findings challenge the theory that the cervix forms the main reservoir of HPV and further indicates that anal cancer screening is likely warranted for WLH regardless of cervical HPV status.

|   | Anal HPV Persistence at Second HPV Visit |                           | P-Value |
|---|--|---------------------------|---------|
|   | Persistence or Change<br>N (Column %)    | Clearance<br>N (Column %) |         |
| <b>Total (Row %)</b>  | 57 (53.8)                                | 19 (17.9)                 |         |
| <b>Age at Anal HPV Visit (Median, IQR)</b>  | 51 (44 - 55)                             | 50 (46 - 56)              | 0.73*   |
| <b>Race/Ethnicity</b>   |  |                           | 0.34**  |
| Black, non-Hispanic   | 30 (52.6)                                | 7 (36.8)                  |         |
| Hispanic  | 15 (26.3)                                | 4 (21.1)                  |         |
| Other Race/Ethnicity  | 7 (12.3)                                 | 5 (26.3)                  |         |
| White, non-Hispanic   | 5 (8.8)                                  | 3 (15.8)                  |         |
| <b>Duration between First and Second Anal HPV Results (Days) (Median, IQR)</b>    | 528 (365 - 902)                          | 595 (478 - 1028)          | 0.30*   |
| <b>HIV Viral Load at Matching HRA Visit (Copies per milliliter) (Median, IQR)</b> | 20 (20 - 48)                             | 20 (20 - 26)              | 0.79*   |
| <b>CD4 Cell Count at Matching HRA Visit (Cells per milliliter) (Median, IQR)</b>  | 684 (411 - 1040)                         | 590 (341 - 743)           | 0.05*   |
| <b>Prevalent HRA HSIL at time of First Anal HPV Visit****</b>                     | 10 (17.5)                                | 0 (0.0)                   | 0.05**  |
| <b>HRA HSIL Incidence (Incidence per 100 person-years) ****</b>                   | 22.15 (16.22, 29.55)                     | 3.03 (0.37, 10.94)        | <0.0001 |
| <b>Receptive Anal Intercourse</b>   |  |                           | 0.89**  |
| Yes   | 37 (64.9)                                | 12 (63.2)                 |         |
| No  | 20 (35.1)                                | 7 (36.8)                  |         |
| <b>Cervical Histology Closest to Anal HPV Visit</b>                               |  |                           | 0.58**  |
| Other   | 1 (1.8)                                  | 0 (0.0)                   |         |
| Benign  | 25 (43.9)                                | 12 (63.2)                 |         |
| CIN 1/VIN 1   | 14 (24.6)                                | 2 (10.5)                  |         |
| CIN 2/VIN 2   | 2 (3.5)                                  | 0 (0.0)                   |         |
| CIN 3/VIN 3   | 2 (3.5)                                  | 0 (0.0)                   |         |
| Cervical Cancer   | 0 (0.0)                                  | 0 (0.0)                   |         |
| <b>Duration between Anal HPV Visit and Cervical Histology Date</b>                | 208 (16 - 1179)                          | 14 (1 - 331)              | 0.59*   |
| <b>History of Abnormal Cervical Cytology at Matching HRA visit</b>                |  |                           | 0.25**  |
| Yes   | 29 (50.9)                                | 8 (42.1)                  |         |
| ASCUS   | 4 (7.0)                                  | 2 (10.5)                  |         |
| LSIL  | 7 (12.3)                                 | 0 (0.0)                   |         |
| HSIL  | 0 (0.0)                                  | 0 (0.0)                   |         |
| No  | 12 (21.1)                                | 8 (42.1)                  |         |
| Unknown   | 5 (8.8)                                  | 1 (5.3)                   |         |
| <b>History of Abnormal Cervical Histology at Matching HRA visit</b>               |  |                           | 0.89**  |
| Yes   | 0 (0.0)                                  | 0 (0.0)                   |         |
| CIN 1/VIN 1   | 1 (1.8)                                  | 0 (0.0)                   |         |
| CIN 2/VIN 2   | 0 (0.0)                                  | 0 (0.0)                   |         |
| CIN 3/VIN 3   | 1 (1.8)                                  | 0 (0.0)                   |         |
| Other   | 1 (1.8)                                  | 0 (0.0)                   |         |
| No  | 2 (3.5)                                  | 1 (5.3)                   |         |
| Unknown   | 52 (91.2)                                | 18 (94.7)                 |         |

HRA: High-Resolution Anoscopy; ASCUS: Atypical Squamous Cell of Undetermined Significance; LSIL: Low-grade Squamous Intraepithelial Lesion; HSIL: High-grade Squamous Intraepithelial Lesion

\* T-Test  
\*\* Chi-Square Test  
\*\*\* HRA Diagnosis of AIN 2 or AIN 3 or SCC up to 1 month prior to or up to 3 months after index anal HPV result  
\*\*\*\* Any HRA diagnosis of AIN 2 or AIN 3 or SCC more than 3 months after index anal HPV OR any HRA diagnosis of AIN 2 or

**474 MULTIPLE HIGH-RISK AND NONVACCINE HPV TYPES IN HIV+ UGANDAN WOMEN ON LONG-TERM ART**

Carol Nakisige<sup>1</sup>, Scott V. Adams<sup>2</sup>, Constance Namirembe<sup>3</sup>, Lazarus Okoko<sup>3</sup>, James Ferrenberg<sup>4</sup>, Andrea Towler<sup>2</sup>, Anna Larsen<sup>5</sup>, Jackson Orem<sup>1</sup>, Corey Casper<sup>4</sup>, Lisa M. Frenkel<sup>5</sup>, Thomas S. Uldrick<sup>2</sup>

<sup>1</sup>Uganda Cancer Institute, Kampala, Uganda, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>Hutchinson Centre Research Institute Uganda, Kampala, Uganda, <sup>4</sup>Infectious Disease Research Institute, Seattle, WA, USA, <sup>5</sup>University of Washington, Seattle, WA, USA

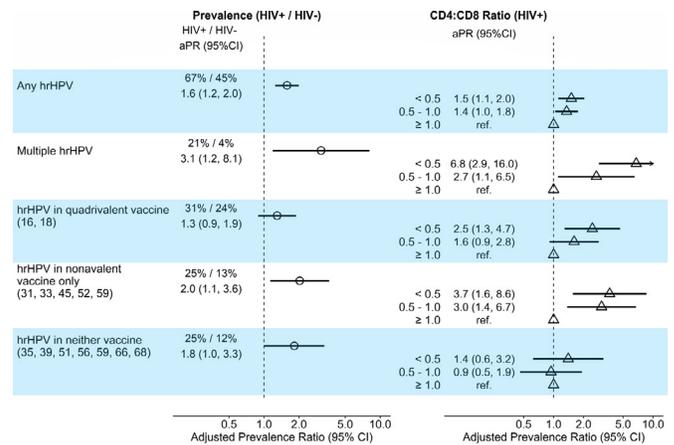
**Background:** Cervical cancer is a leading cause of cancer mortality in sub-Saharan Africa, with increased risk among women living with HIV (WLWH). Improved understanding of the prevalence and distribution of high-risk human papillomavirus (hrHPV) and measures of immune dysfunction among WLWH and cervical abnormalities despite antiretroviral therapy (ART) is required to inform regionally appropriate cervical cancer prevention strategies.

**Methods:** We developed a prospective cohort (2017-2020) of Ugandan WLWH on ART and HIV-seronegative women with abnormalities noted on cervical cancer screening with visual inspection with acetic acid (VIA). Those with VIA+ exams underwent cervical biopsies for histopathologic grading. Cervical brush specimens were tested for hrHPV DNA genotypes. Among WLWH, we further evaluated association between immune, HIV treatment-related, and social risk factors and hrHPV and cervical high grade squamous intraepithelial lesions (HSIL) findings. Associations were evaluated with Poisson regression to estimate adjusted hrHPV prevalence ratios (aPR) with robust 95% confidence intervals (95%CI).

**Results:** Of 16,380 women screened, 815 (5%) were VIA+, and 304 (188 WLWH, 116 HIV-seronegative) had VIA abnormalities large enough for biopsy and consented to participate. Among WLWH, median age was 34 years, ART duration 6 years, CD4 667 cells/μL, and CD4/CD8 ratio 0.9. hrHPV was detected in 67% of WLWH and 45% of HIV-seronegative women (aPR [95%CI], 1.58 [1.25, 2.00]). WLWH had increased detection of multiple hrHPV (aPR [95%CI], 3.10 [1.19, 8.08]), ≥1 hrHPV covered by the nonvalent but not quadrivalent vaccine (aPR [95%CI], 2.0 [1.1, 3.6]), and ≥1hrHPV not covered by any vaccine (aPR [95%CI], 1.8 [1.0, 3.3]). In multivariable analyses among WLWH, lower CD4/CD8 ratio was associated with any hrHPV, multiple hrHPV, and hrHPV in the nonvalent vaccine only (Figure). 29% WLWH vs 9% HIV-seronegative women

had HSIL. HIV viral load 200-1000 copies/mL was associated with HSIL cervical dysplasia.

**Conclusion:** WLWH with cervical abnormalities are at increased risk for prevalent single and multiple hrHPV. Risk is associated with measures of immune dysfunction despite long-term ART. HPV vaccination with the nonavalent HPV is needed for young adolescents in populations at high-risk of HIV infection in sub-Saharan Africa. Optimization of ART and evaluation of additional immune interventions for management of cervical HSIL in WLWH on ART are warranted.



**475 THE PERSISTENCE OF HIV-ASSOCIATED KAPOSI SARCOMA: ANALYSES OF US MEDICARE POPULATION**

Ramya Ramaswami<sup>1</sup>, Nick Williams<sup>2</sup>, Kathryn Lurain<sup>1</sup>, Jomy George<sup>2</sup>, Craig Mayer<sup>2</sup>, Robert Yarchoan<sup>1</sup>, Vojtech Huser<sup>2</sup>

<sup>1</sup>National Cancer Institute, Bethesda, MD, USA, <sup>2</sup>National Institutes of Health, Bethesda, MD, USA

**Background:** Several prospective cohort studies have demonstrated that HIV-associated Kaposi sarcoma (KS) is declining and suggest that its incidence is likely to diminish further. However, these trends may not be present throughout the United States and in all races or age groups over time. Moreover, little is known about individuals with HIV infection and KS receiving care with Medicare. Here, we study changes in demographics and causes of mortality over time among patients with HIV-associated KS enrolled in the Medicare cohort.

**Methods:** We queried the US Medicare dataset between 1999-2017 provided by the Virtual Research Data Center's Chronic Conditions Warehouse. Individuals with an HIV diagnosis (B20, Z21 from ICD10-CM or 042 from ICD9-CM) on any claim in any study year were included. Within this cohort, a subcohort for these analyses included individuals who required care for a KS diagnosis (using 21 diagnostic codes from ICD9-CM and ICD10-CM) within a year group were reported as a distinct individual regardless of the number of times a claim featured a KS diagnosis. Mortality was classified from death certificates and primary cause was described as either ICD Chapters B (Infectious Diseases, including HIV), C (Cancer) and I (Heart Disease). Analyses were divided into 3 eras (1999-2005, 2006-2010, 2011-2017). Statistical analyses of demographic differences by time period were evaluated using Chi square analyses and 2x2 contingency for 1999-2005 compared with 2011-2017.

**Results:** Between 1999-2017, there were 426,352 individuals within HIV Medicare cohort, including 14,046 distinct beneficiaries billing Medicare for KS over all 3 time periods. Patients with HIV-associated KS were predominantly male, but we noted an increase in the proportion of Black patients over time (26% in 1999-2005 to 31% in 2011-2017, P <0.0001, Table 1) and of those between 46-64 years of age (33% in 1999-2005 to 55% in 2011-2017, P <0.0001); impacting an older population over time. The overall proportion of deaths reported of patients with KS during an era increased over time from 36% in 1999-2017 to 44% in 2011-2017 (P<0.0001). Death from KS decreased over time but primary causes of death from cardiovascular diseases and other cancers (lung cancer, hepatocellular cancer and anal cancer) increased.

**Conclusion:** HIV-associated KS remains an important and persistent malignancy with changing demographics and primary causes of death over time within the HIV Medicare cohort.

|                                   |                | 1999-2005 (%) | 2006-2010 (%) | 2011-2017 (%) | P-value*  |
|-----------------------------------|----------------|---------------|---------------|---------------|-----------|
|                                   | Distinct Cases | 7,468         | 4,927         | 5,102         |           |
|                                   | Median Age     | 45            | 49            | 53            | <0.0001   |
| Sex                               | Male           | 6643(88)      | 4310(86)      | 4658(91)      | <0.0001   |
| Race                              | White          | 4389(58)      | 2662 (53)     | 2811(55)      | <0.0001   |
|                                   | Black          | 2012(26)      | 1536(30)      | 1621(31)      | <0.0001   |
| Oldest age observed in study year | 18-25          | 18(<1)        | -             | 22(<1)        | 0.03      |
|                                   | 26-45          | 3883(51)      | 1651(33)      | 1167(22)      | <0.0001   |
|                                   | 46-64          | 2513(33)      | 2391(48)      | 2820(55)      | <0.0001   |
|                                   | 65+            | 1054(14)      | 877(17)       | 1093(21)      | <0.0001   |
|                                   | Mortality      | Deaths        | 2,696(36)     | 1,887(38)     | 2,246(44) |

Table 1: Case Demography of HIV+ patients Presenting with KS within Year Ranges

\*P-value is the comparison of Medicare enrollees with HIV and KS between years 1999-2005 and 2011-2017.

#### 476 HPV GENOTYPE AND FAILURE AFTER TREATMENT OF CERVICAL PRECANCER

Christina Carlander<sup>1</sup>, Camilla Lagheden<sup>1</sup>, Carina Eklund<sup>1</sup>, Sara Nordqvist Kleppe<sup>1</sup>, Mensur Dzabic<sup>1</sup>, Philippe Wagner<sup>2</sup>, Pär Sparén<sup>1</sup>, Joakim Dillner<sup>1</sup>

<sup>1</sup>Karolinska Institute, Stockholm, Sweden, <sup>2</sup>Uppsala University, Uppsala, Sweden

**Background:** Data regarding type-specific HPV and failure after treatment of high-grade cervical intraepithelial neoplasia (CIN2+) in women living with HIV (WLWH) is scarce. The aim was to assess the association between HPV genotype and failure within one year after CIN2+ treatment, in WLWH compared to HIV-negative women.

**Methods:** The Swedish National HIV Registry, the Swedish Population Registry and the Swedish National Cervical Screening Registry were linked. CIN2+ tissue blocks of women living with HIV (WLWH) and HIV-negative women, matched for country of birth (1:2), were retrieved from bio-banks and HPV genotyped. 116 WLWH and 226 HIV negative women were included in the final study population. Adjusted odds ratios (adjOR), stratified by country of birth, were calculated using Conditional logistic regression.

**Results:** The most common HPV-types pre and post-treatment in WLWH with treatment failure were HPV16 and HPV35. The absolute risk of treatment failure in women with pre-treatment HPV16/18 was 26% (95% CI 14-44) in WLWH and 12% in HIV-negative women (95% CI 7-19), with no statistically significant difference by HIV status in conditional regression analysis (adjusted OR [adjOR] 3.2, 95% CI 0.8-12.1). The absolute risk of treatment failure in women with pre-treatment non-HPV16/18 was 20% (95% CI 12-31) in WLWH and 5% in HIV-negative women (95% CI 2-11). WLWH with pre-treatment non-HPV16/18 were eight times more likely to have treatment failure than HIV-negative women (adjOR 7.9, 95% CI 2.1-30.5).

**Conclusion:** HPV16 and 35 were the most common types in WLWH with treatment failure. WLWH with pre-treatment non-HPV16/18 were eight times more likely to have treatment failure than HIV-negative women. This could have implications for surveillance strategies following CIN2+ treatment in WLWH.

#### 477 CERVICAL CANCER PREVENTION DURING COVID-19 PANDEMIC: THE CRES EpiC3-90 PROJECT, ZAMBIA

Mwate J. Chaila<sup>1</sup>, Petronella Lumbala<sup>1</sup>, Memory Kachimbe<sup>1</sup>, Martin Phiri<sup>1</sup>, Bosco Mukanyimi<sup>1</sup>, Linda Mwila Chibesa<sup>1</sup>, Mirriam Selisho<sup>2</sup>, Quagy Siamalambwa<sup>3</sup>, Albert Mwangi<sup>1</sup>, Mwayabo J. Kazadi<sup>1</sup>

<sup>1</sup>Catholic Relief Services, Lusaka, Zambia, <sup>2</sup>Lusaka Provincial Health Office, Lusaka, Zambia, <sup>3</sup>Southern Provincial Health Office, Ministry of Health, Choma, Zambia

**Background:** The Epidemic Control 90-90-90 (EpiC3-90) Project is a U.S Centers for Disease Control & Prevention (CDC) funded project that supports the Ministry of Health (MOH) in Zambia to achieve the UNAIDS 90-90-90 targets in faith-based and Government facilities. The project also supports prevention activities including cervical cancer (CaCx) screening in Women Living with HIV (WLWH). CaCx remains the most frequent cancer in Zambia accounting for about 25% of all new cancer cases annually. It is also the most common cause of cancer related death in the country. EpiC3-90 carried out technical support to the 15 supported districts from April 2020 to September 2020 to improve the CaCx screening in WLWH.

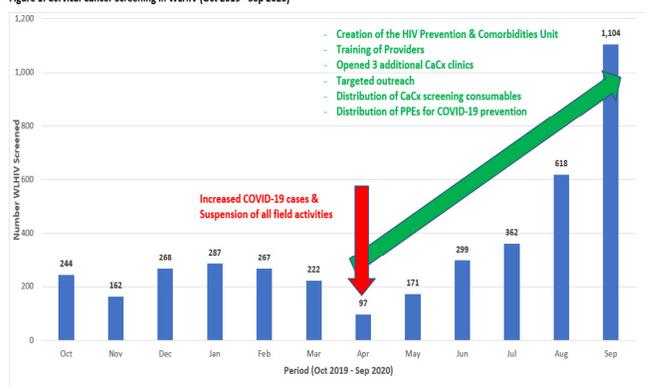
**Methods:** EpiC3-90 created an HIV prevention & comorbidities unit, with adequate staffing to support the establishment of CaCx screening points in

supported regions. Three new screening sites were opened in locations with the largest projected number of WLWH and 43 new providers were trained to staff both new and existing facilities. Community outreach was also carried out in all supported districts. To prevent overcrowding, in view of the COVID-19 pandemic, a staggered appointment system was employed at the sites. Other measures put in place was observance of social distancing, hand washing facilities and ensuring that both the staff and clients were masked-up. Mentorship in documentation and technical support was provided. We present findings from October 2019 to September 2020.

**Results:** The average number of WLWH screened for cervical cancer increased from 242 per month (October 2019 - March 2020) to 442 (April - September 2020) indicating 82.6% improvement. This translated to an increase in the number of WLWH who were screened from 1,450 in the first half of the year to 2,651 in the second half of the year. By September 2020, 4,101 WLWH had been screened for CaCx (Figure 1).

**Conclusion:** It is possible to improve access to safe cervical cancer prevention services during the COVID-19 pandemic in WLWH through a coordinated approach among key stakeholders and service providers. CaCx prevention services need to continue due to its high disease burden in Zambia.

Figure 1: Cervical Cancer Screening in WLWH (Oct 2019 - Sep 2020)



#### 478 TREATMENT TOXICITY FOR LUNG CANCER PATIENTS WITH AND WITHOUT HIV INFECTION

Keith Sigel<sup>1</sup>, Maria Rodriguez-Barradas<sup>2</sup>, Kimberly Stone<sup>1</sup>, Matthew Goetz<sup>3</sup>, Sheldon Brown<sup>4</sup>, Roger Bedimo<sup>5</sup>, Fatma Shebl<sup>6</sup>, Kristina Crothers<sup>7</sup>, Deborah Marshall<sup>1</sup>, Lesley S. Park<sup>8</sup>

<sup>1</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>2</sup>Michael E. DeBakey VA Medical Center, Houston, TX, USA, <sup>3</sup>VA Greater Los Angeles Health Care System, Los Angeles, CA, USA, <sup>4</sup>James J Peters VA Medical Center, Bronx, NY, USA, <sup>5</sup>VA North Texas Health Care Center, Dallas, TX, USA, <sup>6</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>7</sup>Puget Sound VA Medical Center, Seattle, WA, USA, <sup>8</sup>Stanford University, Stanford, CA, USA

**Background:** Lung cancer is the most common cause of cancer death for people with HIV (PWH). Chemotherapy and radiotherapy (RT) are frequently used for lung cancer treatment, but the risk of toxicity from these treatments is unclear for PWH.

**Methods:** We identified lung cancer patients (stage I-III) diagnosed 1998-2017 who received either chemotherapy or RT, from the Veterans Aging Cohort Study using linked cancer registry data. Information on demographics, comorbidity burden, HIV-related biomarkers, VACS index version 2 (V2), first-line cancer treatment and toxicity (using primary diagnosis codes associated with inpatient hospitalizations in the six-month period after chemotherapy and/or RT initiation) were collected from electronic medical record information. We compared characteristics and risk of nine chemotherapy and three RT toxicities, as well as longitudinal white blood cell and hemoglobin levels, by HIV status. We then evaluated predictors of chemotherapy adverse events for PWH by fitting a multivariable logistic model and generating predicted probabilities of toxicity.

**Results:** We identified 263 PWH and 477 uninfected Veterans with lung cancer receiving chemotherapy or RT. Patients were similar by HIV status according to demographics, lung cancer stage and treatment (all p>0.05). More than one-third of patients experienced a toxicity but there were no significant differences in the proportions of hospitalization for chemotherapy or RT toxicity by HIV status. Chemotherapy patients experienced substantial declines in

hemoglobin and white blood cell levels during treatment, but the magnitude also did not differ by HIV status. The median decrease in CD4 count for PWH was 61%, but degree of decline was not associated with risk of toxicity or overall survival. Among PWH, both VACS index V2 (odds ratio [OR]: 1.38; p=0.01) and Charlson comorbidity score (OR 1.38 (p=0.008) were independently associated with chemotherapy toxicity risk after adjusting for age, race, and cancer stage. Predicted probabilities of major adverse chemotherapy outcomes ranged from 6.7% for the lowest VACS index and Charlson comorbidity scores, to 99% for the highest scores.

**Conclusion:** Patients with HIV and lung cancer were not at higher risk of chemotherapy or radiotherapy toxicity compared to uninfected patients. Comorbidity burden and VACS Index scores both predicted major chemotherapy toxicity for lung cancer patients with HIV.

| Table: Chemotherapy and radiotherapy major adverse events following lung cancer treatment by HIV status. |               |                         |      |
|--|---------------|-------------------------|------|
| Adverse Outcome  | Chemotherapy  |                         | p    |
|  | PWH<br>N=263  | HIV uninfected<br>N=477 |      |
| Severe anemia, n (%)   | 23 (13)       | 51 (14)                 | 0.6  |
| Bacteremia, n (%)  | 2 (1)         | 6 (2)                   | 0.6  |
| Bronchitis, n (%)  | 4 (2)         | 12 (3)                  | 0.6  |
| Cellulitis, n (%)  | 1 (1)         | 10 (3)                  | 0.08 |
| Dehydration/Electrolyte imbalance, n (%)   | 15 (8)        | 43 (12)                 | 0.2  |
| Nausea/Emesis, n (%)   | 6 (3)         | 17 (5)                  | 0.4  |
| Pneumonia, n (%)   | 14 (8)        | 27 (8)                  | 0.8  |
| Acute renal failure, n (%)   | 7 (4)         | 25 (7)                  | 0.1  |
| Sepsis, n (%)  | 5 (2)         | 7 (2)                   | 0.6  |
| Any adverse outcome, n (%)   | 64 (35)       | 126 (35)                | 0.9  |
| Median relative WBC decrease after chemotherapy (IQR)  | 67% (51%-78%) | 68% (46%-78%)           | 0.8  |
| Median relative HGB decrease after chemotherapy (IQR)  | 25% (16%-34%) | 25% (16%-35%)           | 0.9  |
| Median relative CD4 decrease after chemotherapy (IQR)  | 61% (35%-76%) |                         |      |
| Radiotherapy   |               | p                       |      |
|  | PWH<br>N=208  | HIV uninfected<br>N=355 |      |
| Esophagitis, n (%)   | 10 (5)        | 9 (3)                   | 0.2  |
| Pneumonitis, n (%)   | 0             | 0                       |      |
| Hemoptysis, n (%)  | 2 (1)         | 2 (1)                   | 0.6  |
| Median relative CD4 decrease after chemoradiotherapy   | 66% (52%-78%) |                         |      |

**479 GYNAECOLOGICAL AND BREAST CANCERS IN WOMEN LIVING WITH HIV IN SOUTH AFRICA**

**Tafadzwa G. Dhokotera**<sup>1</sup>, Mazvita Muchengeti<sup>2</sup>, Maša Davidović<sup>1</sup>, Eliane Rohner<sup>3</sup>, Victor Olago<sup>3</sup>, Matthias Egger<sup>3</sup>, Elvira Singh<sup>2</sup>, Julia Bohlus<sup>1</sup>  
<sup>1</sup>Swiss Tropical and Public Health Institute, Basel, Switzerland, <sup>2</sup>National Health Laboratory Service, Johannesburg, South Africa, <sup>3</sup>University of Bern, Bern, Switzerland

**Background:** In South Africa, the burden of HIV is higher amongst women compared to men with a prevalence of 17%. We aimed to determine the incidence of gynaecological and breast cancers in women living with HIV (WLHIV) in South Africa.

**Methods:** We used data from the South African HIV Cancer Match (SAM) study, a national HIV cohort using HIV laboratory data linked to the National Cancer Registry from 2004 to 2014. We included females aged ≥15 years with at least two HIV-related laboratory records. The outcomes of interest were female specific cancers, specifically Breast, Cervix, Vulva, Vagina, Uterus, Ovary and Placenta cancer according to the International Classification of Disease for Oncology version 3 coding (C50-C58). We determined the overall crude incidence of female specific cancers as well as the individual cancers and the association between female specific cancers and age, CD4 cell counts, calendar period and socio-economic status (SES) at municipal level.

**Results:** From 3,278,510 women and 10.63 million years of follow-up, we identified 14,523 female specific cancers. The median age was 32 years (interquartile range (IQR): 26–40) at first HIV-related test and 43 years (IQR: 36–50) at cancer diagnosis. The median first CD4 cell count was 306 (IQR: 172–474) cells/μL for those without cancer and 263 cells/μL (IQR: 140–424) for those with cancer. The overall crude incidence rate of female specific cancers was 135/100,000 person-years (py). The highest incidence rate was for cervical cancer (83.2/100,000 py), followed by breast (37.2/100,000 py), vulva (5.3/100,000 py), uterine (4.1/100,000 py), ovarian (2.1/100,000 py), vaginal (1.8/100,000 py) and placenta (0.6/100,000 py) cancer. Overall, diagnosis with female specific cancers was associated with low CD4 cell counts (≤200 cells/μL),

older age, early calendar period (2004–2006) and higher municipal SES (Figure 1). The incidence of breast and placenta cancer was not associated with low CD4 cell counts.

**Conclusion:** The incidence of female specific cancers particularly those associated with the Human Papilloma Virus and breast cancer is high amongst WLHIV. Immunodeficiency remains a contributor to cancer development in WLHIV. HIV treatment and cancer screening programmes should continue to be strengthened as a potential prevention measure for female specific cancers in WLHIV. The elevated cancer incidence observed in those with higher SES might reflect differential access to cancer diagnoses in WLHIV in South Africa.

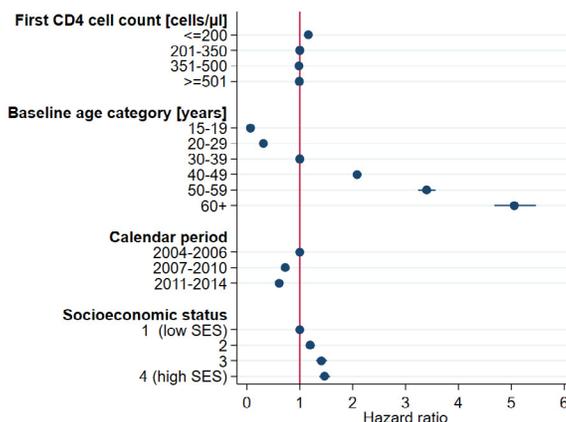


Figure 1: Factors associated with a diagnosis of a female specific cancer in women living with HIV

\*Multivariable Cox proportional hazard model adjusting for first CD4 cell count, age at first HIV-related test, calendar period and municipal socio-economic status (SES)

**480 PHASE 1 STUDY OF LENALIDOMIDE WITH EPOCH AND RITUXIMAB IN PRIMARY EFFUSION LYMPHOMA**

**Kathryn Lurain**<sup>1</sup>, Ramya Ramaswami<sup>1</sup>, Anaida Widell<sup>1</sup>, Irene Ekwede<sup>1</sup>, Ralph Mangusan<sup>1</sup>, Jomy George<sup>2</sup>, Elaine S. Jaffe<sup>1</sup>, Stefania Pittaluga<sup>1</sup>, Maryalice Stetler-Stevenson<sup>1</sup>, Hao-Wei Wang<sup>1</sup>, Mark J. Roth<sup>1</sup>, Vickie A. Marshall<sup>3</sup>, Denise Whitby<sup>3</sup>, Thomas S. Uldrick<sup>1</sup>, Robert Yarchoan<sup>1</sup>

<sup>1</sup>National Cancer Institute, Bethesda, MD, USA, <sup>2</sup>National Institutes of Health, Bethesda, MD, USA, <sup>3</sup>Frederick National Laboratory for Cancer Research, Frederick, MD, USA

**Background:** Primary effusion lymphoma (PEL) is an aggressive B-cell lymphoma strongly associated with HIV that presents as malignant effusions but also as extracavitary masses. It is caused by Kaposi sarcoma herpesvirus (KSHV), which also causes Kaposi sarcoma (KS) and multicentric Castlemann disease (MCD). Prognosis is poor with survival of 10–22 months. Lenalidomide (LEN), an immunomodulatory drug, downregulates IRF4, which is overexpressed in PEL. Etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone and rituximab (EPOCH-R) is safe and effective for CD20+ HIV-associated lymphomas. While PEL is CD20-negative, rituximab eradicates KSHV-infected B-cells, a source of inflammatory cytokines, and is standard treatment for MCD.

**Methods:** In a prospective phase 1 study, we evaluated EPOCH-R and LEN (EPOCH-R2) in untreated PEL for safety. PEL was diagnosed via cytology, flow cytometry and/or biopsy. Participants (pts) received EPOCH-R days 1–5 and LEN 25 mg orally days 1–10 (with dose de-escalation for toxicity) every 21 days for 6 cycles. Pts with leptomeningeal PEL (CSF-PEL) received intrathecal chemotherapy; pts without CSF-PEL received intrathecal prophylaxis. Pts received thromboprophylaxis, opportunistic infection (OI) prophylaxis, and antiretroviral therapy (ART). Adverse events (AEs) were evaluated by CTCAEv5 and responses by Lugano criteria. Response to treatment, immune reconstitution, and overall survival (OS) were evaluated using descriptive statistics, Wilcoxon signed-rank test and Kaplan-Meier methodology.

**Results:** 6 HIV+ cisgender men with stage 4 PEL were enrolled July 2017–August 2019. All received integrase inhibitor-based ART. 4 had concomitant KS; 1 had MCD. Median baseline CD4+ was 231 cells/μL with no significant change at end-of-treatment (p=0.46). The most common grade 3–4 AEs were expected hematologic AEs: grade 4 neutropenia (100%), leukopenia (100%), thrombocytopenia (67%) and CD4+ lymphopenia (67%). No pts developed OIs. There were no dose-limiting toxicities; LEN 25 mg is the recommended phase 2 dose. 1 pt completed only 5 cycles due to progressive disease (PD). 2 pts who

completed 6 cycles died: 1 from PD and 1 from HIV-related complications 5 months after EPOCH-R2. The response rate was 50% (95% CI:11.8–88.1). 2-yr overall survival was 66.7% (95% CI:19.5–90.4).

**Conclusion:** Front-line PEL treatment with EPOCH-R2 was safe with preliminary evidence of activity and good OS and will be further evaluated in the ongoing phase 2 continuation of this trial.

Table 1. Participant Baseline Characteristics, Treatment Responses, and Outcomes

| Participant | Age (years) | HIV VL (copies/mL) | CD4 <sup>+</sup> T-cells/μL | Disease Category       | ECOG | CSF Involvement | Concurrent KSHV-diseases | Response after C2 | Response EOT | Long-term Outcome        | Δ CD4 <sup>+</sup> T-cells/μL |
|-------------|-------------|--------------------|-----------------------------|------------------------|------|-----------------|--------------------------|-------------------|--------------|--------------------------|-------------------------------|
| 1           | 50          | 112                | 200                         | Extracavitary          | 1    | No              | None                     | PR                | CR           | CR                       | -31                           |
| 2           | 49          | 0                  | 262                         | Extracavitary          | 1    | Yes             | None                     | PR                | CR           | CSF Relapse <sup>†</sup> | +28                           |
| 3           | 41          | 0                  | 10                          | Effusion               | 3    | No              | KS                       | PR                | CR           | CR                       | +46                           |
| 4           | 35          | 0                  | 310                         | Effusion/extracavitary | 2    | Yes             | KS                       | PR                | PD           | CR*                      | -86                           |
| 5           | 27          | 422                | 3                           | Effusion               | 2    | Yes             | KS                       | SD                | SD           | Death                    | +1                            |
| 6           | 29          | 33                 | 403                         | Effusion               | 4    | No              | KS, MCD                  | PR                | -            | Death                    | -193                          |

C indicates cycle; CR, complete response; CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; KS, Kaposi sarcoma; KSHV, Kaposi sarcoma herpesvirus; MCD, multicentric Castleman disease; PR, partial response; PD, progressive disease; SD, stable disease.  
<sup>†</sup>Participant 2 received additional therapy after EPOCH-R2 for CSF relapse. He was alive at time of censor with persistent CSF disease and no evidence of systemic relapse.  
<sup>\*</sup>Participant 4 received additional therapy after EPOCH-R2 resulting in CR.

#### 481 ALTERED TUMOR MICROENVIRONMENT AND REDUCED SURVIVAL IN HIV+ HEAD AND NECK CANCERS

Syim Salahuddin<sup>1</sup>, Margaret Wu<sup>1</sup>, Javier Perez Irizarry<sup>2</sup>, Teresita Vega<sup>2</sup>, Natalia Isaeva<sup>3</sup>, Kurt Schalper<sup>1</sup>, Wendell G. Yarbrough<sup>3</sup>, Brinda Emu<sup>1</sup>

<sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>Yale New Haven Hospital, New Haven, CT, USA,

<sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Background:** Incidence of non-AIDS-defining cancers, including head and neck cancer (HNC), is rising among people living with HIV (PLWH) in the HAART era.

The following study compares demographics, clinical outcomes, and the tumor microenvironment of HIV+ and Uninfected HNC patients at a single institution.

**Methods:** Yale Tumor Registry query identified 3,488 HNC patients, including 50 with HIV, for analysis (Clinical Cohort, 2002-2018). In addition, quantitative immunofluorescence (QIF) was performed on tumor tissue from 22 HIV+ and 75 matched Uninfected patients (Tissue Cohort).

**Results:** Within our clinical cohort, 76.0% of HIV+ and 71.9% of Uninfected patients were male, with HIV+ patients being younger (55.5 vs. 62.0,  $p < 0.0001$ ). Both HIV+ and Uninfected groups reported high rates of past/current tobacco use (82.0% and 71.6%, respectively) and alcohol consumption (64.0% and 61.1%, respectively). Non-Hispanic Whites comprised 82.1% of the Uninfected group, while Non-Hispanic Blacks were the most prevalent group (44.0%) among HIV+ patients, followed by Non-Hispanic Whites (40.0%) and Hispanics (16.0%). 87.9% of the HIV+ patients were on HAART, with 69.7% achieving viral loads  $\leq 50$  copies/mL and a median CD4 count of 345 cells/mm<sup>3</sup>. The majority in both groups had advanced stage (III, IV) compared to early stage (0, I, II) tumors at diagnosis (Table 1). The most prevalent HNC anatomic site among HIV+ patients was the oropharynx (OP), followed by lip/oral cavity and larynx. Among tested OP cases, 70.0% of HIV+ and 70.1% of Uninfected patients were HPV positive. There was decreased 1-yr overall survival in the HIV+ group compared to the Uninfected group (76.0 vs. 85.5%,  $p = 0.06$ ), which was significant among those with early stage disease (69.2% vs. 94.0%,  $p = 0.0002$ ). Within our tissue cohort, QIF of the tumor microenvironment revealed that HIV+ patients had lower CD8+ T cell infiltration ( $p = 0.04$ ), and lower PD-L1 expression in both the tumor ( $p = 0.01$ ) and macrophage ( $p = 0.002$ ) compartments compared to Uninfected patients. No difference in PD-1 expression was noted.

**Conclusion:** HNC patients with HIV were significantly younger compared to the general HNC population, and experienced lower 1-yr survival with early stage disease. CD8 T cell infiltration and PD-L1 expression, which are associated with improved outcomes, appear lower among PLWH. Further evaluation of HIV-HNC subgroups, with detailed analysis of tumor site, HPV status and treatment disparities, is warranted to better delineate differences in outcome.

|                                  |                 | HIV+ (n=50) | Uninfected (n=3438) |
|----------------------------------|-----------------|-------------|---------------------|
| Stage at cancer diagnosis, n (%) | Stage 0         | 0 (0%)      | 78 (2.27%)          |
|                                  | Stage I         | 4 (8.00%)   | 691 (20.1%)         |
|                                  | Stage II        | 9 (18.0%)   | 425 (12.4%)         |
|                                  | Stage III       | 11 (22.0%)  | 545 (15.9%)         |
|                                  | Stage IV        | 22 (44.0%)  | 1536 (44.7%)        |
|                                  | Stage unknown   | 4 (8.00%)   | 163 (4.74%)         |
| Anatomic site, n (%)             | Lip/Oral Cavity | 13 (26.0%)  | 1230 (35.8%)        |
|                                  | Oropharynx      | 21 (42.0%)  | 1170 (34.0%)        |
|                                  | Nasopharynx     | 0 (0%)      | 75 (2.2%)           |
|                                  | Hypopharynx     | 3 (6.0%)    | 178 (5.2%)          |
|                                  | Larynx          | 13 (26.0%)  | 717 (20.9%)         |

482



#### H3K27me3 PREVENTS ABERRANT TRANSCRIPTION AND EPISOME CLEARANCE OF KSHV

Simon Weissmann<sup>1</sup>, Adam Grundhoff<sup>1</sup>

<sup>1</sup>Heinrich Pette Institute, Hamburg, Germany

**Background:** Introduction: The double stranded DNA virus KSHV (Kaposi sarcoma associated herpes virus) is the causative agent of a number of human neoplasms. It can establish lifelong chronic infections resulting in persistent reservoirs of latently infected cells. Viral latency as well as lytic reactivation of KSHV represent processes that are primarily regulated at the epigenetic level, in particular via histone modifications. Tri-methylation of histone H3 at lysine residue 27 (H3K27me3), mediated by the polycomb repressive complex 2 (PRC2), and ubiquitination of H2A lysine 119 (H2AK119Ub), mediated by the polycomb repressive complex 1 (PRC1), are associated with transcriptionally repressed chromatin and can be found on KSHV episomes early after viral entry and chromatinisation. Objectives: We want to investigate the role of H3K27me3 and H2AK119Ub in KSHV gene repression and to elucidate the impact of polycomb loss on the viral life cycle.

**Methods:** Here we present a cellular model for complete PRC2 depletion and investigate the effects of H3K27me3 loss in KSHV biology

**Results:** Depletion of SUZ12, the structural component of the core PRC2 complex, causes a complete loss of H3K27me3 and its precursor modifications H3K27me2 and H3K27me1. Surprisingly, we observed reduced but still significant levels of H2AK119Ub, arguing that PRC1 can be recruited to KSHV independently of PRC2 activity. Furthermore, we demonstrate that loss of H3K27 methylation leads to histone hyperacetylation of KSHV episomes, supporting an active chromatin state, which ultimately leads to aberrant transcription of broad regions of the viral genome. In cells, which support KSHV's lytic lifecycle, this state of spurious transcription led to a lytic reactivation and production of viral progeny. Interestingly, when lytic reactivation was suppressed, ablation of PRC2 led to a drastic reduction of episome maintenance, resulting in increased episome loss during cell division.

**Conclusion:** We will discuss the potential mechanism of viral transcriptional derepression, how the absence of H3K27me3 may cause increased KSHV episome clearance, and whether increased viral transcription and episome loss are interdependent. Importantly, the availability of highly specific small molecule inhibitors against the catalytic subunit of PRC2 provides the possibility of a therapeutic intervention aiming at forced KSHV clearance.

483

#### PLWH AND CANCER EXHIBIT UNIQUE PATTERN OF ACTIVATED AND EXHAUSTED CD8+ T CELLS

Omkar Chaudhary<sup>1</sup>, Diane Trotta<sup>1</sup>, Xiuping Chu<sup>2</sup>, Chip Bradley<sup>2</sup>, Xun Wang<sup>2</sup>, Jason Okulicz<sup>3</sup>, Ryan C. Maves<sup>4</sup>, Karl Kronmann<sup>5</sup>, Christina Schofield<sup>6</sup>, Jason Blaylock<sup>2</sup>, Brian Agan<sup>2</sup>, Anuradha Ganesan<sup>2</sup>, Brinda Emu<sup>1</sup>

<sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>Uniformed Services University of the Health Sciences, Bethesda, MD, USA, <sup>3</sup>Brooke Army Medical Center, San Antonio, TX, USA, <sup>4</sup>Naval Medical Center San Diego, San Diego, CA, USA, <sup>5</sup>Naval Medical Center Portsmouth, Portsmouth, VA, USA, <sup>6</sup>Madigan Army Medical Center, Tacoma, WA, USA

**Background:** Non-AIDS-defining cancers (NADC) are increased in incidence in people living with HIV (PLWH). We have shown that CD8+ T cells co-expressing PD-1, CD160, and CD244 are higher in PBMCs of PLWH with cancer compared to those without cancer. Expression of transcription factors T-bet and Eomesodermin (Eomes) is associated with T-cell exhaustion. This study evaluates whether HIV-infected cancer patients exhibit altered expression of T-bet and Eomes, particularly among those cells expressing multiple inhibitory receptors.

**Methods:** 25 cancer cases (lymphoma, lung cancer and HPV-associated malignancies in those with durable viral suppression) and 87 controls were identified from the United States Military HIV Natural History Study (NHS)

repository; Controls were matched for CD4+ count, duration of HIV infection and viral suppression. Markers of differentiation (CD45RA, CCR7), inhibitory receptors (PD-1, CD160, CD244, TIGIT, LAG-3), activation (HLADR, CD38) and transcriptional factors (T-bet and Eomes) were measured using flow cytometry. Upon staphylococcal enterotoxin B stimulation, CD8+ T-cell function was measured (CD107a, granzyme, perforin, TNFα and IFNγ production)

**Results:** The proportion of CD8+ T cells that are T-betdimEomeshi, was higher among cases compared to controls. Cells co-expressing PD-1, CD160, and CD244 (triple-positive) had the highest expression of a T-betdimEomeshi phenotype compared to single and dual-positive subsets (p<0.0001 for all comparisons). Among subsets of cells with differential expression of inhibitory receptors, the proportion of T-betdimEomeshi expression was higher between cases and controls among triple-positive (87.4%vs.79.8%, cases vs controls, p=0.001) and dual-positive subsets (PD-1+CD160-CD244+: 61.6%vs.53.6%,p=0.02 and PD-1-CD160+CD244+: 75.9%vs. 68.2 %,p=0.03). Upon stimulation, triple-positive cells retained granzyme and perforin production but at lower levels compared to PD-1-CD160+CD244+ subset. Furthermore, triple-positive cells retained IFNγ and TNFα secretion but lower than those expressing only PD-1 (Fig. 1).

**Conclusion:** Among PLWH with virologic suppression, those with cancer have higher percentages of cells with co-expression of three inhibitory receptors. This subset is distinct in its functional profile compared to those that only express 1 or 2 receptors. Furthermore, these defined subsets of cells have a differential expression among cancer patients, suggesting underlying changes in T-cell biology in response to the presence of a cancer.

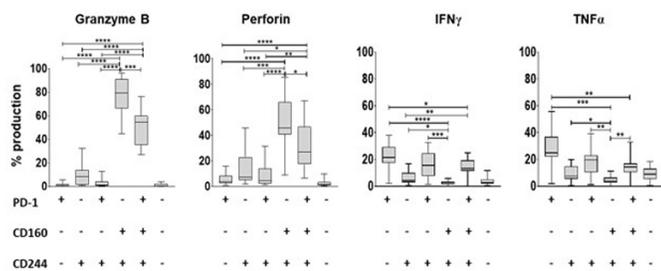


Figure 1- Granzyme, perforin IFNγ, and TNFα production by CD8+ T cells co-expressing PD-1, CD160 and CD244.

**484 TRENDS IN CANCER INCIDENCE AMONG PEOPLE LIVING WITH HIV IN ONTARIO, CANADA, 1997-2018**

**Ioana Nicolau<sup>1</sup>, Tony Antoniou<sup>2</sup>, Jennifer Brooks<sup>1</sup>, Rahim Moineddin<sup>1</sup>, Curtis Cooper<sup>3</sup>, Michelle Cotterchio<sup>4</sup>, Jennifer Gillis<sup>1</sup>, Claire Kendall<sup>5</sup>, Abigail Kroch<sup>6</sup>, Zak Knowles<sup>7</sup>, Joanne Lindsay<sup>2</sup>, Colleen Price<sup>8</sup>, Kate Salters<sup>9</sup>, Marek Smieja<sup>10</sup>, Ann N. Burchell<sup>2</sup>**

<sup>1</sup>University of Toronto, Toronto, Canada, <sup>2</sup>St Michael's Hospital, Toronto, Canada, <sup>3</sup>Ottawa Hospital Research Institute, Ottawa, Canada, <sup>4</sup>Cancer Care Ontario, Toronto, Canada, <sup>5</sup>Bruyère Research Institute, Ottawa, Canada, <sup>6</sup>Ontario HIV Treatment Network, Toronto, Canada, <sup>7</sup>Community AIDS Treatment Information Exchange, Toronto, Canada, <sup>8</sup>Ontario Advisory Committee on HIV/AIDS, Toronto, Canada, <sup>9</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, <sup>10</sup>McMaster University, Hamilton, Canada

**Background:** With combination antiretroviral therapy (cART), there has been a decrease in AIDS-defining cancers (ADC), however, some jurisdictions have reported increases in non-AIDS defining cancers (NADC). We sought to confirm these findings in Ontario, Canada, a province with the highest number of people living with HIV nationally and in a setting with universal access to health care.

**Methods:** We conducted a population-based retrospective cohort study of adults (≥18 years) living with HIV using health administrative data including the provincial cancer registry. Participants were followed for incident cancers from January 1, 1997 to Dec 31, 2018. Cancers were grouped as infection-related (ADC and infection-related NADC) and infection-unrelated cancers (all other NADC). Age-standardized incidence rates (aIR) per 1,000 person-years (PY) with 95% confidence intervals (CI) were calculated using direct standardization, and stratified by sex and calendar period, using the 2011 Canadian population as the reference population. The Cochran-Armitage trend test was used to examine trends across calendar periods.

**Results:** Among 17,675 individuals (78% males) followed for 166,616 PY, 1127 first primary incident cancers were diagnosed (531 [47%] infection-unrelated

cancers and 596 [53%] infection-related cancers). The incidence of any cancer over the entire study period ranged from 8.8 per 1,000 PY (95% CI 3.8, 17.3) in 1997-1999 to 7.4 per 1,000 PY (6.4, 8.4) in 2016-2018 (Table 1). Infection-related cancer rates declined from 9.6 per 1,000 PY (3.8, 19.9) in 1997-1999 to 2.5 per 1,000 PY (2.0, 3.2) in 2016-2018 (p-trend 0.035). In contrast, infection-unrelated cancer incidence increased in the early cART era (1997-2003) and remained relatively stable until 2016-2018 (aIR 4.8 [4.0, 5.7] per 1,000 PY) (p-trend 0.396). When stratified by sex (Table 1), the incidence of infection-unrelated cancers among females increased and surpassed the incidence in males in 2016-2018 (aIR females: 7.02 [4.98, 9.62] vs. aIR males: 4.17 [3.36, 5.13]).

**Conclusion:** Our findings that infection-related cancer rates declined whereas infection-unrelated cancers increased could be a result of improved cART and increased longevity as the life expectancy of people with HIV approaches that of the general population. This study confirms that ongoing surveillance of cancer incidence among people with HIV using population-based estimates are needed to locally inform cancer prevention and care services planning.

Table 1. Age-standardized incidence of cancers per 1,000 person-years among people with HIV, by calendar period and sex, Ontario, Canada

| Calendar period                    | Females                   |         | Males                     |         | Both Sexes Combined       |         |
|------------------------------------|---------------------------|---------|---------------------------|---------|---------------------------|---------|
|                                    | aIR per 1,000 PY (95% CI) | P-trend | aIR per 1,000 PY (95% CI) | P-trend | aIR per 1,000 PY (95% CI) | P-trend |
| 1997-1999                          | 2.09 (0.18, 8.52)         | 0.049   | 10.56 (4.27, 21.68)       | 0.279   | 8.80 (3.81, 17.32)        | 0.224   |
| 2000-2003                          | 5.00 (1.71, 11.33)        |         | 9.89 (6.84, 13.84)        |         | 8.89 (6.35, 12.12)        |         |
| 2004-2007                          | 7.42 (3.98, 12.63)        |         | 10.47 (8.14, 13.25)       |         | 9.91 (7.90, 12.28)        |         |
| 2008-2011                          | 8.24 (5.42, 12.02)        |         | 8.96 (7.36, 10.82)        |         | 8.87 (7.45, 10.48)        |         |
| 2012-2015                          | 7.91 (5.70, 10.69)        |         | 7.22 (6.07, 8.52)         |         | 7.36 (6.33, 8.50)         |         |
| 2016-2018                          | 8.59 (6.38, 11.32)        |         | 7.05 (5.97, 8.26)         |         | 7.36 (6.38, 8.45)         |         |
| <b>All years</b>                   | <b>8.10 (6.83, 9.55)</b>  |         | <b>8.19 (7.52, 8.90)</b>  |         | <b>8.17 (7.57, 8.79)</b>  |         |
| <b>Infection-related cancers</b>   |                           |         |                           |         |                           |         |
| Calendar Period                    | 0.486                     |         | 0.053                     |         | 0.035                     |         |
| 1997-1999                          | 0.54 (0.01, 3.03)         | 0.057   | 9.19 (3.20, 20.64)        | 0.613   | 9.56 (3.77, 19.91)        | 0.396   |
| 2000-2003                          | 2.25 (0.62, 5.77)         |         | 4.39 (2.81, 6.52)         |         | 3.87 (2.60, 5.53)         |         |
| 2004-2007                          | 2.08 (0.64, 4.99)         |         | 5.12 (3.70, 6.91)         |         | 4.63 (3.45, 6.08)         |         |
| 2008-2011                          | 2.34 (1.23, 4.06)         |         | 4.50 (3.44, 5.78)         |         | 3.89 (3.08, 4.86)         |         |
| 2012-2015                          | 3.19 (1.82, 5.19)         |         | 3.22 (2.51, 4.07)         |         | 3.24 (2.61, 3.97)         |         |
| 2016-2018                          | 1.57 (0.83, 2.69)         |         | 2.87 (2.19, 3.69)         |         | 2.54 (2.01, 3.16)         |         |
| <b>All years</b>                   | <b>2.38 (1.77, 3.14)</b>  |         | <b>3.82 (3.40, 4.27)</b>  |         | <b>3.46 (3.13, 3.83)</b>  |         |
| <b>Infection-unrelated cancers</b> |                           |         |                           |         |                           |         |
| Calendar Period                    | 0.057                     |         | 0.613                     |         | 0.396                     |         |
| 1997-1999                          | 1.55 (0.04, 8.63)         | 0.057   | 1.37 (0.37, 3.51)         | 0.613   | 1.25 (0.41, 2.89)         | 0.396   |
| 2000-2003                          | 2.74 (0.39, 9.32)         |         | 5.50 (3.04, 9.17)         |         | 4.96 (2.88, 7.95)         |         |
| 2004-2007                          | 5.35 (2.43, 10.21)        |         | 5.34 (3.58, 7.66)         |         | 5.37 (3.81, 7.36)         |         |
| 2008-2011                          | 5.90 (3.41, 9.51)         |         | 4.47 (3.30, 5.91)         |         | 4.74 (3.67, 6.04)         |         |
| 2012-2015                          | 4.72 (3.09, 6.90)         |         | 3.99 (3.11, 5.04)         |         | 4.15 (3.35, 5.06)         |         |
| 2016-2018                          | 7.02 (4.98, 9.62)         |         | 4.17 (3.36, 5.13)         |         | 4.77 (3.99, 5.67)         |         |
| <b>All years</b>                   | <b>5.72 (4.62, 7.00)</b>  |         | <b>4.37 (3.86, 4.93)</b>  |         | <b>4.64 (4.17, 5.15)</b>  |         |

**485 IMMUNODEFICIENCY AND CANCER IN 3.4 MILLION PEOPLE LIVING WITH HIV IN SOUTH AFRICA**

**Yann Ruffieux<sup>1</sup>, Mazvita Muchengeti<sup>2</sup>, Matthias Egger<sup>1</sup>, Orestis Efthimiou<sup>1</sup>, Lina Bartels<sup>1</sup>, Victor Olago<sup>2</sup>, Maša Davidović<sup>1</sup>, Tafadzwa G. Dhokotera<sup>1</sup>, Julia Bohlius<sup>1</sup>, Elvira Singh<sup>2</sup>, Eliane Rohner<sup>1</sup>**

<sup>1</sup>Institute of Social and Preventive Medicine, Bern, Switzerland, <sup>2</sup>National Institute for Communicable Diseases, Johannesburg, South Africa

**Background:** The mechanisms through which HIV infection increases cancer risk are not well understood. We analyzed associations between immunodeficiency and cancer incidence in a nationwide cohort of people living with HIV (PLWH) in South Africa.

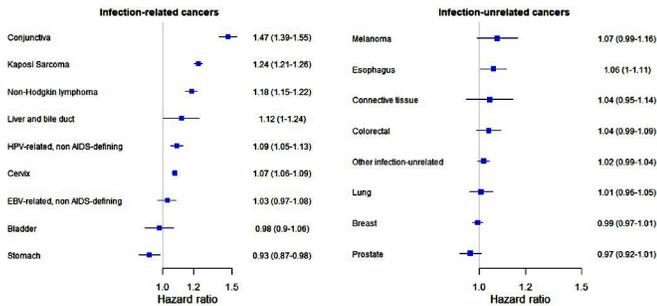
**Methods:** The South African HIV Cancer Match (SAM) Study is a nationwide cohort of PLWH in South Africa. It results from a linkage between HIV-related laboratory test records from the National Health Laboratory Services and cancer diagnoses from the National Cancer Registry for the period 2004-2014. Adults aged 18 years or over from this cohort with at least one year of follow-up after their first CD4 measurement were included. We examined associations between time-updated CD4 cell count and incidence rates of various infection-unrelated and infection-related cancers (further classified by underlying infectious agent). We estimated the adjusted hazard ratios (aHR) for cancer incidence, per 100 CD4 cells/μl decrease using Cox proportional hazards models. Models were adjusted for sex, age, calendar year, and comorbidity with other cancers. We assessed whether sex modified the association between CD4 cell count decrease and cancer incidence.

**Results:** Of 3,454,651 PLWH, 15,059 developed cancer (overall incidence rate: 168/100,000 person-years [py]). The most common cancers were cervical cancer (4,146 cases; 62/100,000 py), Kaposi sarcoma (2,259 cases; 25/100,000 py), and non-Hodgkin lymphoma (1,058 cases; 12/100,000 py). The association between low CD4 cell count and higher cancer incidence was strongest for conjunctival cancer (aHR per 100 CD4 cells/μl decrease: 1.47, 95% confidence interval [CI] 1.39-1.55), Kaposi sarcoma (aHR 1.24, 95% CI 1.21-1.26), and non-Hodgkin lymphoma (aHR 1.18, 95% CI 1.15-1.22), see Figure. Among infection-unrelated cancers, low CD4 cell counts were associated with higher rates of esophageal

cancer (aHR 1.06, 95 CI 1.00-1.11), but not breast, lung, or prostate cancer. The association between immunodeficiency and cancer incidence was stronger in women than in men for Kaposi Sarcoma (aHR 1.27 vs 1.18,  $p$ -value testing for interaction: 0.005) and non-Hodgkin lymphoma (aHR 1.22 vs. 1.12,  $p=0.007$ ).

**Conclusion:** Low CD4 cell count was associated with an increased risk of developing various infection-related cancers among PLWH. Preventing HIV-induced immunodeficiency may be a potent cancer control strategy among PLWH in sub-Saharan Africa, a region heavily burdened by cancers attributable to infections.

Adjusted hazard ratios for cancer incidence with associated 95% confidence intervals, per 100 CD4 cells/ $\mu$ l decrease. EBV: Epstein-Barr virus; HPV: Human papillomavirus



EBV-related, non-AIDS-defining cancers include Hodgkin lymphoma and nasopharyngeal cancer. HPV-related, non-AIDS-defining cancers include anal, penile, vaginal, vulvar, and some head and neck cancers.

#### 486 HIGHER BURNOUT OF ONCOLOGY PROVIDERS COMPARED WITH HIV PROVIDERS IN KENYA

**Devon McMahon**<sup>1</sup>, Helen Byakwaga<sup>2</sup>, Aggrey Semeere<sup>3</sup>, Miriam Laker-Oketta<sup>2</sup>, Linda Chemtai<sup>3</sup>, Sonya Prasad<sup>4</sup>, Ingrid V. Bassett<sup>5</sup>, Naftali Busakhala<sup>3</sup>, Jeffrey N. Martin<sup>6</sup>, Esther Freeman<sup>5</sup>

<sup>1</sup>Harvard Medical School, Boston, MA, USA, <sup>2</sup>Infectious Disease Institute, Kampala, Uganda, <sup>3</sup>Moi University, Eldoret, Kenya, <sup>4</sup>Mt Sinai School of Medicine, New York, NY, USA, <sup>5</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>6</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** In sub-Saharan Africa (SSA), the burden of HIV-associated malignancies remains high despite the scale-up of antiretroviral therapy (ART). Oncology providers in SSA are limited in number and manage patients with high complexity and often poor outcomes. However, little is known about the differences in burnout among oncology providers compared to HIV providers who often co-manage patients with HIV-associated malignancies.

**Methods:** We approached all clinical officers and nurses working in either an oncology referral clinic or one of three representative primary care clinics for HIV medicine in the AMPATH network in western Kenya from August 2019–January 2020. Burnout was measured using the self-administered 22-item Maslach Burnout Inventory (MBI) for Medical Personnel Health Services Survey adapted for the sub-Saharan African context. MBI uses sub-scales of depersonalization (scores 0 to 30, higher indicates more burnout), personal accomplishment (scores 0 to 48, higher indicates less burnout), and emotional exhaustion (scores 0 to 54, higher indicates more burnout) (Thorsen BMC Nursing; 2011; Kim PLoS One 2018). In linear regression analyses we used directed acyclic graphs to assess the determinants of burnout.

**Results:** Of 89 healthcare workers enrolled (23 oncology providers, 66 HIV providers), the majority (58%) were female, the median age was 37 (IQR 31–43) years and 57% were clinical officers and 43% nurses. On the depersonalization, personal accomplishment, and emotional exhaustion scales the median scores for oncology providers were 4 (IQR 2–7), 41 (IQR 32–46) and 17 (IQR 8–28) respectively, compared to 1 (IQR 0–4), 42 (IQR 39–47) and 14 (IQR 8–21) for HIV providers. After adjusting for age, gender, provider type, hours worked per week, and commute time, the mean score on the depersonalization scale for oncology providers was 2.8 units higher ( $p=0.006$ ) than HIV providers, on the personal accomplishment scale 3.5 units lower for oncology providers ( $p=0.03$ ) compared to HIV providers, and not significantly different for emotional exhaustion ( $p=0.55$ ) (Table 1).

**Conclusion:** Oncology providers in Kenya had higher burnout measurements compared to HIV providers. Quantifying the factors underlying oncology provider burnout may allow health systems in SSA to identify solutions to

improve provider working environments and care delivery for patients with HIV-associated malignancies.

**Table 1:** Evaluation of potential determinants of three domains of healthcare provider burnout: depersonalization, personal accomplishment, and emotional exhaustion burnout scores. All variables adjusted for other variables in column.

| Characteristic                           | Domains of Maslach Burnout Index  |   |  |
|--|---|---|--|
|  | Mean unit difference in depersonalization scale $\beta$ (95% CI; $p$ value) | Mean unit difference in personal accomplishment scale $\beta$ (95% CI; $p$ value) | Mean unit difference in emotional exhaustion scale $\beta$ (95% CI; $p$ value) |
| Patient care responsibility              |   |   |  |
| HIV primary care                         | Ref   | Ref   | Ref  |
| Oncology                                 | +2.8** (0.83 to 4.81; $p=0.006$ )   | -3.5* (-6.5 to -0.44; $p=0.03$ )  | +1.6 (-3.7 to 7.0; $p=0.55$ )  |
| Age, per 10 year increment               | +0.38 (-0.67 to 1.44; $p=0.47$ )  | -0.87 (-2.48 to 0.74; $p=0.27$ )  | +2.7 (-0.11 to 5.5; $p=0.06$ )   |
| Gender                                   |   |   |  |
| Female                                   | Ref   | Ref   | Ref  |
| Male                                     | +0.85 (-1.05 to 2.75; $p=0.38$ )  | -0.47 (-3.4 to 2.4; $p=0.75$ )  | -1.9 (-7.0 to 3.2; $p=0.46$ )  |
| Provider type                            |   |   |  |
| Clinical officer                         | Ref   | Ref   | Ref  |
| Nurse                                    | +1.42 (-0.60 to 3.4; $p=0.17$ )   | -0.97 (-4.1 to 2.1; $p=0.53$ )  | +0.95 (-4.4 to 6.3; $p=0.73$ )   |
| Work time per week, per 5 hour increment | 0.01 (-1.00 to 1.01; $p=0.99$ )   | +0.63 (-0.91 to 2.17; $p=0.42$ )  | +0.07 (-2.62 to 2.76; $p=0.96$ )   |
| Commute time, per 1 hour increment       | +3.81* (0.50 to 7.11; $p=0.02$ )  | -1.26 (-6.32 to 3.79; $p=0.62$ )  | -1.38 (-10.2 to 7.46; $p=0.78$ )   |

\* $p<0.05$

\*\* $p<0.01$

487



#### RISK OF CANCER BY HIV STATUS AND BIRTH REGION: A NATIONWIDE REGISTER-BASED STUDY

**Stina Malmström**<sup>1</sup>, Philippe Wagner<sup>2</sup>, Aylin Yilmaz<sup>3</sup>, Pär Sparén<sup>4</sup>, Veronica Svedhem<sup>4</sup>, Christina Carlander<sup>4</sup>

<sup>1</sup>Västmanland County Hospital, Västerås, Sweden, <sup>2</sup>Uppsala University, Uppsala, Sweden, <sup>3</sup>Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, <sup>4</sup>Karolinska Institute, Stockholm, Sweden

**Background:** There is a lack of register-based cancer cohort studies in people living with HIV (PLWH) that include a HIV-negative comparison group and the possibility to control for socioeconomic factors on an individual level. We aimed to examine cancer risk in the entire Swedish population categorized by HIV status, sex at birth and birth region.

**Methods:** The study population consisted of all people in Sweden, born 1940–2000 ( $n = 8\,587\,629$ ), identified from the Swedish Total Population register and linked to the Swedish National HIV Register (InfCareHIV), the Swedish National Cancer Register and the Longitudinal Integration Database for Health Insurance and Labour Market Studies. The cohort was followed for three consecutive periods (1988–1997, 1998–2007, and 2008–2017). Adjusted Hazard Ratio (adjHR) of cancer (infection/non-infection-related) was calculated for each time period using Cox regression analyses, categorized by HIV-status, sex at birth, and birth region, adjusted for age and income. Separate models for PLWH only were categorized by sex at birth and adjusted for age, income, birth region, nadir CD4, HIV-RNA, and mode of HIV-transmission.

**Results:** The proportion of cancer attributable to infection decreased over time in PLWH but was still over 40% in 2008–2017 (46% in women, 48% in men) compared to 11% in HIV-negative people. Risk of infection-related cancer was higher in PLWH than in HIV-negative people for all time periods, irrespective of sex at birth and birth region, with the highest risk seen among men in 1988–1997 (adjHR 39.0, 95% CI 33.6–45.3, ref HIV-negative men). In PLWH, infection-related cancer was associated with male sex, nadir CD4 < 200, and history of intravenous drug use (the latter for women only). There was no significant difference in risk of non-infection-related cancer by HIV status in men. Women with HIV had decreased risk of non-infection-related cancer in 1998–2007 (adjHR 0.3, 95% CI 0.1–0.7, ref HIV-neg women 1998–2007) but no significant difference was seen in the periods before or after.

**Conclusion:** In this nation-wide cancer-register study the risk of infection-related cancer remained higher in PLWH compared to HIV-negative people over time, irrespective of sex at birth and birth region, and was associated with level of immunosuppression and history of intravenous drug use. Early HIV detection and early antiretroviral therapy remain crucial for the prevention of cancer in this population.

**Table 1. Risk of infection-related and non-infection related cancer in Sweden, categorized by HIV status and sex**

| Period of follow-up                             | 1988-1997                  |                            | 1998-2007                |                          | 2008-2017               |                         |
|---|----------------------------|----------------------------|--------------------------|--------------------------|-------------------------|-------------------------|
|   | Crude HR                   | adjHR <sup>1</sup>         | Crude HR                 | adjHR <sup>2</sup>       | Crude HR                | adjHR <sup>2</sup>      |
| <b>Infection-related cancer<sup>3</sup></b>     |                            |                            |                          |                          |                         |                         |
| Men with HIV <sup>4</sup>                       | <b>33.8</b><br>(29.1-39.2) | <b>39.0</b><br>(33.6-45.3) | <b>8.2</b><br>(6.5-10.4) | <b>9.3</b><br>(7.3-11.7) | <b>5.9</b><br>(4.9-7.2) | <b>6.3</b><br>(5.1-7.6) |
| Women with HIV <sup>5</sup>                     | <b>6.2</b><br>(3.4-11.1)   | <b>7.6</b><br>(4.2-13.7)   | <b>2.6</b><br>(1.3-4.9)  | <b>3.3</b><br>(1.7-6.3)  | <b>3.5</b><br>(2.5-5.0) | <b>4.7</b><br>(3.3-6.6) |
| <b>Non infection-related cancer<sup>6</sup></b> |                            |                            |                          |                          |                         |                         |
| Men with HIV <sup>4</sup>                       | 1.2<br>(0.7-1.8)           | 1.4<br>(0.9-2.2)           | 0.6<br>(0.4-0.8)         | 0.8<br>(0.5-1.1)         | 0.8<br>(0.7-1.0)        | 1.0<br>(0.8-1.2)        |
| Women with HIV <sup>5</sup>                     | 0.2<br>(0.1-0.8)           | 0.3<br>(0.1-1.3)           | 0.1<br>(0.1-0.4)         | 0.3<br>(0.1-0.7)         | 0.5<br>(0.4-0.7)        | 0.9<br>(0.7-1.3)        |

<sup>1</sup>Adjusted for age at inclusion and birth region. <sup>2</sup>Adjusted for age at inclusion, birth region and annual income at time of inclusion. <sup>3</sup>Kaposi's sarcoma, Hodgkin's lymphoma, non-Hodgkin lymphoma, HPV-related (anal, vaginal, vulval, cervical, penile, oral/pharyngeal), liver, merkel-cell carcinoma and gastric. <sup>4</sup>Ref. HIV-negative men. <sup>5</sup>Ref. HIV-negative women. <sup>6</sup>Remaining cancers. Statistically significant numbers in bold. HR: hazard ratio, adjHR: adjusted hazard ratio.

**488 ASSOCIATION BETWEEN INTEGRASE INHIBITORS (INSTIs) AND CARDIOVASCULAR DISEASE (CVD)**

**Bastian Neesgaard**, for the RESPOND Study Group  
*Rigshospitalet, Copenhagen, Denmark*

**Background:** While associations between use of older antiretroviral drug (ARV) classes and CVD are well described, there are limited data related to use of INSTIs.

**Methods:** RESPOND participants were followed from latest of cohort enrolment or 1. Jan. 2012 (baseline) to the earliest of first CVD event (myocardial infarction [MI], stroke or invasive cardiovascular procedure [ICP]), last follow-up (FU) or 1. Oct. 2018. Logistic regression tested associations between 10-year D:A:D CVD risk score and starting an INSTI. To assess associations between CVD and INSTI exposure, multivariable negative binomial regression models were adjusted for demographics, traditional CVD risk factors, HIV-related factors, antiretroviral treatment (ART) status and concomitant or prior use of ARVs associated with CVD; where appropriate, variables were time-updated (figure footnote).

**Results:** Of 21267 included individuals, 46% were exposed to one or more INSTIs during FU (2147 to raltegravir, 2385 to elvitegravir and 6372 to dolutegravir). Compared to low baseline D:A:D CVD risk, odds of starting an INSTI were higher for those with a medium and high risk (odds ratio, 95% confidence interval, CI; 1.1 [1.0-1.2] and 1.2 [1.1-1.4]), though not reaching significance for those with a very high risk (1.1 [0.9-1.2]). During a median 6.3 years of FU (interquartile range 3.5-6.7; 106,870 person-years, PYFU), 517 individuals experienced a CVD event (incidence rate, IR, 4.9/1000 PYFU [4.5-5.3]: 210 MIs, 162 strokes, 145 ICPs). The crude CVD IR increased from 4.5/1000 PYFU [3.9-4.8] in those with no INSTI exposure to 10.7/1000 PYFU [8.1-13.8] at >0-6 months and decreased steadily thereafter (Figure). After adjustment, compared to those never exposed, the IR ratios of CVD peaked at >0-6 months of INSTI exposure (2.5 [1.9-3.4]) but were comparable to those unexposed thereafter (p < 0.01, Figure). Results were consistent in models adjusting only for D:A:D CVD risk score, and models excluding ICP events or individuals with prior CVD. There was no interaction between INSTI exposure group and age (p=0.3) or D:A:D CVD risk strata (P=0.6)

**Conclusion:** In the large RESPOND collaboration use of INSTIs was associated with an increased incidence of CVD in the first 6 months of exposure after accounting for known CVD risk factors including the ART backbone and across a wide range of sensitivity analyses. While we cannot fully exclude possible channeling bias or residual confounding, these findings call for further investigations.

**Table 1. Risk of infection-related and non-infection related cancer in Sweden, categorized by HIV status and sex**

| Period of follow-up                             | 1988-1997                  |                            | 1998-2007                |                          | 2008-2017               |                         |
|---|----------------------------|----------------------------|--------------------------|--------------------------|-------------------------|-------------------------|
|   | Crude HR                   | adjHR <sup>1</sup>         | Crude HR                 | adjHR <sup>2</sup>       | Crude HR                | adjHR <sup>2</sup>      |
| <b>Infection-related cancer<sup>3</sup></b>     |                            |                            |                          |                          |                         |                         |
| Men with HIV <sup>4</sup>                       | <b>33.8</b><br>(29.1-39.2) | <b>39.0</b><br>(33.6-45.3) | <b>8.2</b><br>(6.5-10.4) | <b>9.3</b><br>(7.3-11.7) | <b>5.9</b><br>(4.9-7.2) | <b>6.3</b><br>(5.1-7.6) |
| Women with HIV <sup>5</sup>                     | <b>6.2</b><br>(3.4-11.1)   | <b>7.6</b><br>(4.2-13.7)   | <b>2.6</b><br>(1.3-4.9)  | <b>3.3</b><br>(1.7-6.3)  | <b>3.5</b><br>(2.5-5.0) | <b>4.7</b><br>(3.3-6.6) |
| <b>Non infection-related cancer<sup>6</sup></b> |                            |                            |                          |                          |                         |                         |
| Men with HIV <sup>4</sup>                       | 1.2<br>(0.7-1.8)           | 1.4<br>(0.9-2.2)           | 0.6<br>(0.4-0.8)         | 0.8<br>(0.5-1.1)         | 0.8<br>(0.7-1.0)        | 1.0<br>(0.8-1.2)        |
| Women with HIV <sup>5</sup>                     | 0.2<br>(0.1-0.8)           | 0.3<br>(0.1-1.3)           | 0.1<br>(0.1-0.4)         | 0.3<br>(0.1-0.7)         | 0.5<br>(0.4-0.7)        | 0.9<br>(0.7-1.3)        |

<sup>1</sup>Adjusted for age at inclusion and birth region. <sup>2</sup>Adjusted for age at inclusion, birth region and annual income at time of inclusion. <sup>3</sup>Kaposi's sarcoma, Hodgkin's lymphoma, non-Hodgkin lymphoma, HPV-related (anal, vaginal, vulval, cervical, penile, oral/pharyngeal), liver, merkel-cell carcinoma and gastric. <sup>4</sup>Ref. HIV-negative men. <sup>5</sup>Ref. HIV-negative women. <sup>6</sup>Remaining cancers. Statistically significant numbers in bold. HR: hazard ratio, adjHR: adjusted hazard ratio.

**489 INFLAMMATORY AND ATHEROGENESIS MARKERS 148 WEEKS POSTSWITCH TO DTG+RPV IN SWORD-1/-2**

**Josep María Llibre<sup>1</sup>**, Luis Fernando López Cortés<sup>2</sup>, Alicia Aylott<sup>3</sup>, Brian Wynne<sup>4</sup>, Jessica Matthews<sup>4</sup>, Jean A. Van Wyk<sup>5</sup>, Lesley P. Kahl<sup>5</sup>

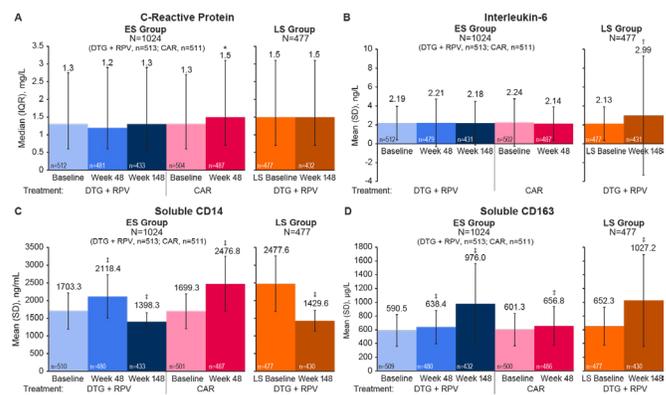
<sup>1</sup>Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, <sup>2</sup>Hospital Universitario Virgen del Rocío, Sevilla, Spain, <sup>3</sup>GlaxoSmithKline, Uxbridge, UK, <sup>4</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>5</sup>ViiV Healthcare, Brentford, UK

**Background:** The SWORD studies demonstrated noninferiority post-switch to the 2-drug regimen (2DR) dolutegravir (DTG) + rilpivirine (RPV) vs 3- or 4-drug current antiretroviral therapy (CAR) at Week (W) 48 and maintained viral suppression to W148. Evaluation of whether switching from CAR to DTG+RPV influences markers of inflammation and atherogenesis is an area of current interest.

**Methods:** Adults with suppressed HIV-1 RNA were randomized to DTG+RPV (Early Switch [ES] group) or continue CAR. CAR participants (pts) suppressed at W48 switched to DTG+RPV at W52 (Late Switch [LS] group). Biomarkers of inflammation and atherogenesis were evaluated from Baseline (BL) to W48 for DTG+RPV and CAR and non-comparatively for DTG+RPV post-switch through W148.

**Results:** 1024 pts were randomized across both studies and exposed to DTG+RPV (n=513) or CAR (n=511). Regarding inflammatory markers through W48, participants on CAR had a greater increase in sCD14 (P<0.0001) vs those on DTG+RPV. No other significant changes from BL to W48 were observed between pts receiving DTG+RPV and CAR. Longitudinally to W148, no significant change in C-reactive protein was observed in the ES and LS groups. Increases in the ES group in sCD14 at W48 and W100 and decreases in the LS group at W100 were observed, although both groups showed significant decreases in sCD14 at W148 (P<0.001). A similar inconsistent pattern of change was observed longitudinally in ES and LS groups for interleukin-6 and sCD163; however, pooled SWORD data showed significant increases in sCD163 at W148 in both groups (P<0.001). Overall, no consistent reproducible pattern of change was seen post-switch across markers (Figure). Regarding atherogenesis markers, in both SWORD studies, FABP-2 and sVCAM-1 for the ES and LS groups showed consistent significant, sustained reductions post-switch to DTG+RPV through W148 (P<0.001) except for a nonsignificant reduction in sVCAM-1 in the ES group at W48. Change from BL to W148 in D-dimer was inconsistent across SWORD-1/-2 and the ES and LS groups at W100; however, significant increases from BL at W148 (P<0.001) was observed in both groups across both studies.

**Conclusion:** In the controlled ES phase, no significant differences between arms were observed at W48 except for sCD14 favoring DTG+RPV. Longitudinally up to W148, there was no consistent, reproducible pattern of change post-switch, providing no evidence of increased inflammation or atherogenesis markers on the 2-drug regimen, DTG+RPV, while maintaining viral suppression.



CAR, current antiretroviral regimen; DTG, dolutegravir; ES, Early Switch; LS, Late Switch; RPV, rilpivirine. P values for C-reactive protein were derived from median values using a 1-sample Wilcoxon signed rank test and represent change from Baseline. P values for interleukin-6, soluble CD14, and soluble CD163 were derived from mean values using a 1-sample 2-sided t test and represent change from Baseline. LS Baseline. Only significant changes (P<0.05) at each time point are noted. \*P<0.035. \*\*P<0.003. \*\*\*P<0.001.

**490 QUINOLINIC ACID IS ASSOCIATED WITH CAROTID INTIMA-MEDIA THICKNESS IN HIV**

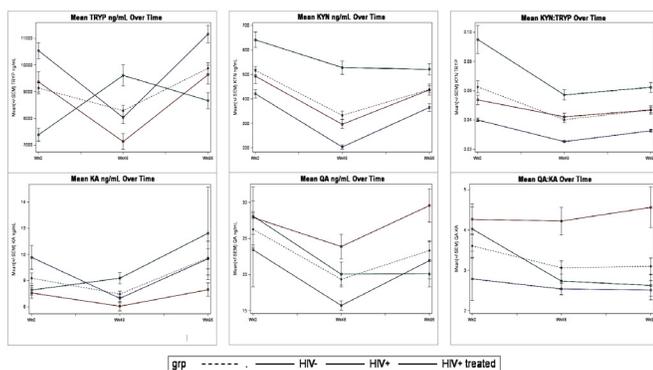
**Corrilynn O. Hileman**<sup>1</sup>, Trong-Tuong Nguyen<sup>1</sup>, Jared C. Durieux<sup>2</sup>, Daniela Schlatter<sup>3</sup>, Xiaolin Li<sup>3</sup>, Grace A. McComsey<sup>2</sup>  
<sup>1</sup>MetroHealth Medical Center, Cleveland, OH, USA, <sup>2</sup>University Hospitals Cleveland Medical Center, Cleveland, OH, USA, <sup>3</sup>Case Western Reserve University, Cleveland, OH, USA

**Background:** Tryptophan (TRYP) metabolism via the kynurenine (KYN) pathway has been implicated in the pathogenesis of cardiovascular disease. Downstream metabolites kynurenic acid (KA) and quinolinic acid (QA) are paths for TRYP degradation that may affect risk differently. Inflammatory pathways mediating these effects have not been studied in HIV.

**Methods:** TRYP, KYN, KA and QA were quantified by LC/MS/MS from adults with and without HIV enrolled in a longitudinal study of carotid intima media thickness (IMT) progression. hsCRP, IL6, sTNF-RI and -RII, ICAM-1 and VCAM-1, D-Dimer and fibrinogen were quantified by ELISA. Data through week 96 was included. Linear mixed effects modeling with stratified propensity score matched on age, sex, race, smoking and BMI was utilized. Direct and indirect effects of inflammation markers were tested where associations between TRYP metabolites and IMT were significant.

**Results:** 123 adults were included (47 HIV+ initiating ART; 31 HIV+ remaining ART-naïve; 45 HIV-). Median age was 40 yrs; 73% male; with BMI 27 kg/m<sup>2</sup>. There were more blacks and current/former smokers in HIV+ (59 vs 27% and 68 vs 31%; both p<0.01). HIV duration (4 yrs) and HIV-1 RNA (2461 copies/ml) were similar among HIV+, but nadir CD4+ was lower in HIV+ initiating ART (340 vs 505 cells/mm<sup>3</sup>; p<0.01). There were differences in TRYP metabolites between groups at baseline and over time (Figure). Notably, in HIV+ initiating ART group, both steepness and at times direction of change in the first year after ART initiation were different from HIV+ remaining ART-naïve and HIV-. Baseline QA and QA:KA ratio (trend) were associated with higher time-updated common carotid artery (CCA) IMT (p=0.05; p=0.04 and p=0.04; p=0.06), but effects attenuated with adjustment (p=0.04; p=0.07 and p=0.03; p=0.11). Baseline QA, KYN and KYN:TRYP ratio (trend) were associated with higher time-updated carotid bulb IMT even with adjustment (QA: p=0.07; p=0.04, KYN: p=0.14; p<0.05 and KYN:TRYP ratio: p=0.1; p=0.09). sTNF-RII, D-Dimer and fibrinogen mediated the effect between QA and CCA IMT, while IL6, sTNF-RI and fibrinogen mediated the effect between QA and bulb IMT; no mediators between KYN and bulb IMT were identified.

**Conclusion:** QA, but not KA, was associated with both CCA and bulb IMT, and inflammatory and coagulation markers appear to mediate these effects. Also, TRYP metabolites were associated more closely with bulb IMT, the site with the highest inflammatory milieu. ART initiation appears to impact TRYP metabolite levels.



**491 HIV INFLAMMATORY PATHWAYS DIFFER ACCORDING TO SOCIOECONOMIC INDICES IN MALAWI**

**Christine Kelly**<sup>1</sup>, Willard Tinago<sup>1</sup>, Dagmar Alber<sup>2</sup>, Patricia Hunter<sup>2</sup>, Alejandro Garcia-Leon<sup>1</sup>, Raphael Kamng'ona<sup>3</sup>, Irene Sheha<sup>3</sup>, Mishek Chamudzi<sup>3</sup>, Kondwani Jamb<sup>3</sup>, Jane Mallewa<sup>4</sup>, Alicia Rapala<sup>2</sup>, Patrick Mallon<sup>1</sup>, Nigel Klein<sup>2</sup>, Henry Mwandumba<sup>3</sup>, Saye Khoo<sup>5</sup>

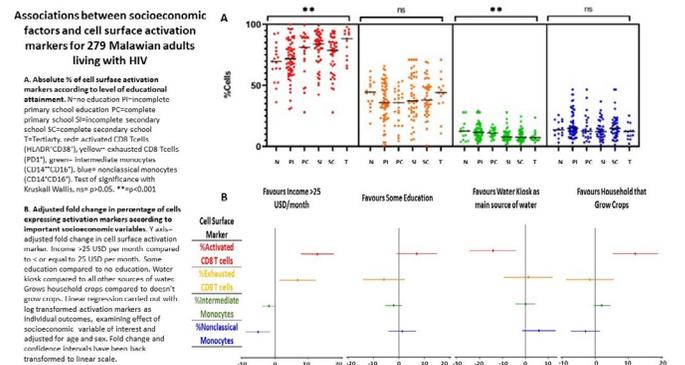
<sup>1</sup>University College Dublin, Dublin, Ireland, <sup>2</sup>University College London, London, UK, <sup>3</sup>Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi, <sup>4</sup>University of Malawi, Blantyre, Malawi, <sup>5</sup>University of Liverpool, Liverpool, UK

**Background:** The role of socioeconomic (SE) indices in immune activation among PLWH is unknown, especially in low income sub Saharan Africa (SSA), where the burden of non-communicable diseases (NCDs) is high.

**Methods:** Malawian adults with CD4<100 cells/ul starting ART in the REALITY trial (NCT01825031), and volunteers without HIV infection, had clinical assessment, socioeconomic evaluation, blood draw for cell surface and soluble activation markers, and carotid femoral pulse wave velocity (cfPWV) carried out at 2 and 42 weeks post-ART initiation. Linear regression models analysed SE associations with i) immune activation markers and ii) arterial stiffness.

**Results:** Of 279 PLWH, median (IQR) age was 36 (31-43) years and 122 (44%) were female. At baseline, T cell activation was more pronounced among those with higher SE indices. CD8 activation increased from 70% amongst those with no education to 88% amongst those with a tertiary education (p=0.002); and from 71% amongst those earning less than 10 USD/month to 87% amongst those earning between 100-150 USD/month (p=0.0001, Figure 1). Adjusting for age and sex, CD8 activation and exhaustion were higher amongst those earning >25 USD/month [fold change 12.7%, p<0.0001 and 6.77%, p=0.016 respectively]. CD8 activation was lower for water kiosk users [70% versus 81%, p=0.002] who also displayed lower rates of CMV PCR positivity [5(7%) versus 57(31%); p<0.0001]. Conversely, monocyte activation was associated with lower SE indices. In adjusted analysis, nonclassical and intermediate monocytes were lower amongst the higher income bracket (fold change -5.23, p=0.006 and -1.91, p=0.063 respectively). Participants with an earth floor displayed expanded nonclassical monocyte populations (p=0.04), but experienced a reduction after 42 weeks of ART [median change -2.2% versus 5.8%, p=0.026]. SE indices independently associated with arterial stiffness (adjusted for age, sex, blood pressure and haemoglobin) were: car ownership [fold change 1.3m/s (95% CI 1.10 to 1.56); p=0.003]; television ownership [1.12m/s (1.03 to 1.23); p=0.012]; and electricity access [1.09m/s (1.01 to 1.17); p=0.029].

**Conclusion:** For PLWH with high SE indices, a sedentary lifestyle combined with HIV driven T cell activation may increase vascular damage. For PLWH with low SE indices, innate immune stress - likely driven by infection, malnutrition, and poor water hygiene - is the predominant inflammatory pathway. Understanding these pathways and their drivers will help target interventions for NCDs.



**492 ASSESSING PROTEIN BIOMARKERS' ROLE IN CVD RISK PREDICTION IN PERSONS WITH HIV (PWH)**

**Sandra E. Safo**<sup>1</sup>, Lillian M. Haine<sup>1</sup>, Jason Baker<sup>2</sup>, Cavan Reilly<sup>1</sup>, Daniel Duprez<sup>2</sup>, James Neaton<sup>1</sup>, Mamta K. Jain<sup>3</sup>, Alejandro Arenas-Pinto<sup>4</sup>, Jiuzhou Wang<sup>1</sup>, Mark N. Polizzotto<sup>5</sup>, Therese Staub<sup>6</sup>

<sup>1</sup>University of Minnesota, Minneapolis, MN, USA, <sup>2</sup>Hennepin County Medical Center, Minneapolis, MN, USA, <sup>3</sup>University of Texas Southwestern, Dallas, TX, USA, <sup>4</sup>UCL Institute of Clinical Trials & Methodology, London, United Kingdom, <sup>5</sup>University of New South Wales, Sydney, Australia, <sup>6</sup>Luxembourg Hospital Center, Luxembourg City, Luxembourg

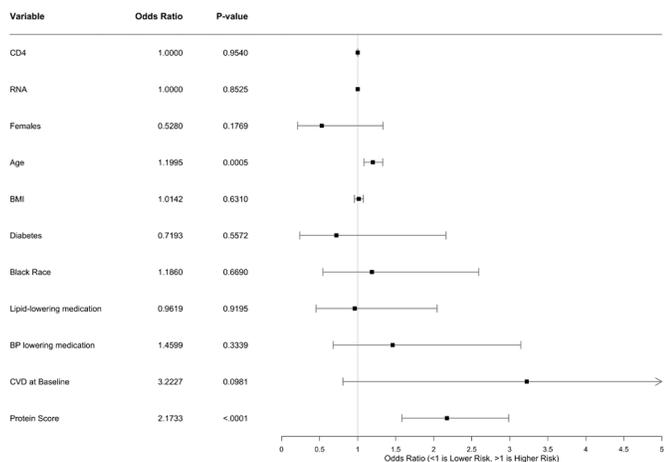
**Background:** PWH have higher rates of CVD than the general population yet CVD risk prediction models rely on traditional risk factors and fail to capture the heterogeneity of CVD risk in PWH. The purpose of this study was to identify protein biomarkers that are able to discriminate between CVD cases and controls in PWH, and to assess if a protein score can predict CVD risk beyond traditional risk factors in PWH

**Methods:** We analyzed 459 baseline protein expression levels from five OLINK panels in a matched CVD (MI, coronary revascularization, stroke, CVD death) case-control study with 390 PWH from INSIGHT trials (131 cases, 259 controls). We filtered out proteins that did not differentiate cases from controls (p-value >0.05); 107 proteins remained. We formed 200 training datasets via bootstrap. For each bootstrap training set, a two-component partial least squares discriminant model (PLSDA) was fit. The importance of each variable in the discrimination of cases and controls in the PLSDA projection was assessed by the variable importance in projection (VIP) score. Proteins with average VIP scores > 1 were used in penalized logistic regression models with elastic net penalty, and proteins were ranked based on the number of times the protein had a nonzero coefficient. Proteins in the top 25th percentile were considered to have high discrimination. A protein score (PS) of the top-ranked proteins was developed using the bootstrap training (for weights) and the entire data.

**Results:** Participants had mean age 47 years, bmi 24.6 kg/m<sup>2</sup>, 13% were females, 4.9% had CVD at baseline and 69% were on ART at baseline. Eight proteins including the hepatocyte growth factor and interleukin-6 were identified as able to distinguish between CVD cases and controls within PWH. The PS was found to be predictive of CVD independent of established CVD and HIV factors (Odds ratio: 2.17, CI: 1.58-2.99). A model with the PS and traditional risk factors had a 5.9% improvement in AUC over the baseline model (AUC=0.731 vs 0.69), which is an increase in model predictive power of 18%. Individuals with a PS above the median score were 3.1 (CI: 1.83- 5.41) times more likely to develop CVD than those with a protein score below the median score.

**Conclusion:** A PS improved discrimination of PWH with CVD and those without, and helped identify PWH with high risk for developing CVD. If validated, this score could be used in addition with established factors to identify CVD at-risk individuals who might benefit from aggressive risk-reduction.

Forest Plot of Coefficients from Logistic Regression Model



**493 ENDOTHELIAL MICROVESICLES: BIOMARKER & MEDIATOR OF ENDOTHELIAL DYSFUNCTION WITH HIV-1**

**Vinicius Pacheco Garcia**<sup>1</sup>, L M. Brewster<sup>1</sup>, Kelly A. Stockelman<sup>1</sup>, Hannah K. Fandl<sup>1</sup>, John W. Treuth<sup>1</sup>, Noah M. DeSouza<sup>1</sup>, Cindy S. Firnhaber<sup>2</sup>, Jared J. Greiner<sup>1</sup>, Brian L. Stauffer<sup>2</sup>, Elizabeth Connick<sup>1</sup>, Christopher A. DeSouza<sup>1</sup>

<sup>1</sup>University of Colorado Boulder, Boulder, CO, USA, <sup>2</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA

**Background:** Clinical interest in circulating endothelial cell derived extracellular microvesicles (EMVs) has increased due to their role in the etiology of endothelial dysfunction and the development and progression of cardiovascular disease (CVD). We have previously reported that circulating EMVs are elevated in HIV-1-seropositive adults and may contribute to endothelial dysfunction and CVD with HIV-1-infection. EMVs released under disease conditions have been shown to negatively affect endothelial nitric oxide synthase (eNOS) resulting in diminished NO bioavailability and impaired vasodilatory function. The experimental aims of this study were to determine: 1) whether circulating EMVs are associated with HIV-1-related endothelial vasodilator dysfunction; and 2) the effects of EMVs isolated from HIV-1-seropositive adults on endothelial cell NO production, in vitro.

**Methods:** Twenty-four sedentary, adults were studied: 12 healthy (9M/3F; 55±2 yr) and 12 HIV-1-seropositive adults on stable antiretroviral therapy (9M/3F; 53±2 yr). All subjects were non-obese, normotensive, normolipidemic, and free of overt cardiometabolic disease. Circulating EMV (CD31+/42b-) number was determined by flow cytometry. Forearm blood flow (FBF: via plethysmography) was assessed by intra-arterial infusion of acetylcholine and sodium nitroprusside. Human umbilical vein endothelial cells were cultured and treated with EMVs (CD144-PE) isolated from the healthy and seropositive adults.

**Results:** Circulating EMVs were ~45% higher (P<0.05) in the HIV-1-seropositive (107±7 EMV/μL) vs healthy (74±7 EMV/μL) adults. FBF responses to acetylcholine were significantly lower (~20%) in the seropositive adults (from 4.1 ± 0.3 to 12.2 ± 0.8 mL/100 mL tissue/min vs 4.3 ± 0.4 to 15.6 ± 0.9 mL/100 mL tissue/min). EMVs were strongly and inversely associated with the vasodilator response to acetylcholine (r=-0.47; p<0.05). Expression of phosphorylated eNOS (20.9±2.3 vs 32.8±2.4 AU) and NO production (6.2±0.5 vs 9.0±0.2 μmol/L) was lower in cells treated with EMVs from the seropositive vs healthy adults. EMV-induced changes in p-eNOS and NO production in vitro were associated with the vasodilation response in vivo (r=0.58 and r=0.51; p<0.05, respectively).

**Conclusion:** Circulating EMVs are not only a biomarker, but also a mechanistic mediator, of endothelial dysfunction with HIV-1. EMVs represent a potential therapeutic target for improving endothelial function and thereby reducing CVD risk in HIV-1 infected adults.

**494 CORONARY ARTERY DISEASE, TRADITIONAL RISK, AND INFLAMMATION AMONG PWH IN REPRIEVE**

**Udo Hoffmann**<sup>1</sup>, Michael T. Lu<sup>1</sup>, Borek Foldyna<sup>1</sup>, Markella V. Zanni<sup>1</sup>, Tricia H. Burdo<sup>2</sup>, Carl Fichtenbaum<sup>3</sup>, E. Turner Overton<sup>4</sup>, Judith A. Aberg<sup>5</sup>, Judith S. Currier<sup>6</sup>, Craig A. Sponseller<sup>7</sup>, Kathleen Melbourne<sup>8</sup>, Pamela S. Douglas<sup>9</sup>, Heather J. Ribaldo<sup>10</sup>, Thomas Mayrhofer<sup>1</sup>, Steven Grinspoon<sup>1</sup>

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>Temple University, Philadelphia, PA, USA, <sup>3</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>5</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>6</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>7</sup>Kowa Pharmaceuticals America, Inc, Montgomery, AL, USA, <sup>8</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>9</sup>Duke Clinical Research Institute, Durham, NC, USA, <sup>10</sup>Harvard TH Chan School of Public Health, Boston, MA, USA

**Background:** REPRIEVE is a large ongoing primary prevention trial of people with HIV (PWH), at risk for cardiovascular disease (CVD). The REPRIEVE Mechanistic Substudy, designed to determine unique factors contributing to CVD in PWH, assesses coronary artery disease (CAD) by coronary CTA and critical pathways of arterial inflammation and immune activation. Comprehensive data from the baseline exam establish the plaque phenotype in this key population.

**Methods:** The study enrolled PWH, 40-75 yrs, without known CVD, on stable ART, with low to moderate risk of atherosclerotic cardiovascular disease (ASCVD) by the 2013 ACC/AHA pooled cohort equation. Coronary CTA data were analyzed across ASCVD risk strata and in regression models including biomarkers: insulin, MCP-1, IL-6, sCD14, sCD163, LpPLA2, oxLDL and hsCRP.

**Results:** Participants (n=755, 31 US sites) were 51±6 yrs, 16% female, 46% non-white, 24% Latinx with CD4 636±275 cells/mm<sup>3</sup>, and well-controlled viremia

(88%, 23% vulnerable plaque (VP), and 16% high Leaman score >5 (LS). A minority had CAC>400 (2%) or luminal stenosis ≥50% (3%). Overall plaque burden included significant non-calcified plaque. Extent of CAD increased with ASCVD risk (Figure) but plaque (30%) and VP (13%) were seen even among participants with ASCVD risk <2.5%. MCP-1, IL-6, LpPLA2, and oxLDL were higher in those with plaque. hsCRP was higher in those with VP and LS >5. In fully adjusted modeling, including ASCVD risk score, significant associations were: 1) LpPLA2 with presence of plaque, CAC>0 and LS >5, 2) MCP-1 and IL-6 with presence of plaque, 3) hsCRP with LS>5. HIV indices were generally not significant in modeling. In subgroup analyses (< or ≥7.5% ASCVD risk), LpPLA2 associated with CAD in those with lower risk. In contrast, oxLDL and hsCRP most consistently associated with CAD in those with higher risk, with significant interaction terms.

**Conclusion:** In this primary prevention cohort with well-controlled HIV, we demonstrate a unique CAD phenotype, including a high prevalence of non-calcified non-obstructive and vulnerable plaque, associated with increased immune activation and arterial inflammation, independent of ASCVD risk. These data suggest the importance of developing tailored CVD prevention strategies targeting inflammation and immune activation in addition to traditional risk in this population.

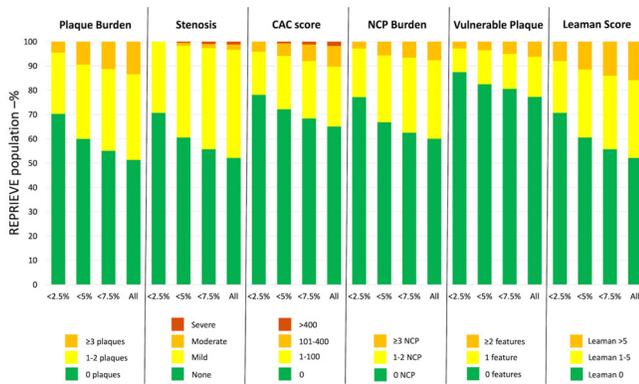


Figure 1: CAD indices by ASCVD Risk Strata. NCP = Non calcified plaque. Overall and non-calcified plaque burden based on number of involved segments/participant. Leaman Score is based on extent, composition, and distribution of plaque.

#### 495 TREATED HIV INFECTION AND PROGRESSION OF CAROTID ATHEROSCLEROSIS IN RURAL UGANDA

**Mark Siedner**<sup>1</sup>, Prosy Bibangambah<sup>2</sup>, June-Ho Kim<sup>1</sup>, Alexander Lankowski<sup>3</sup>, Jonathan L. Chang<sup>1</sup>, Isabelle T. Yang<sup>4</sup>, Douglas S. Kwon<sup>1</sup>, Crystal M. North<sup>1</sup>, Virginia A. Triant<sup>1</sup>, Chris T. Longenecker<sup>5</sup>, Brian Ghoshhajra<sup>1</sup>, Linda Hemphill<sup>1</sup>, Samson Okello<sup>2</sup>, for the UGANDAC Study Team

<sup>1</sup>Harvard Medical School, Boston, MA, USA, <sup>2</sup>Mbarara University of Science and Technology, Mbarara, Uganda, <sup>3</sup>University of Washington, Seattle, WA, USA, <sup>4</sup>Geisel School of Medicine at Dartmouth, Hanover, NH, USA, <sup>5</sup>Case Western Reserve University, Cleveland, OH, USA

**Background:** Studies from the United States have demonstrated HIV to be an independent risk factor for cardiovascular disease (CVD). Although approximately 70% of the world's population of people living with HIV (PLWH) reside in sub-Saharan Africa, there are minimal prospective data on the contributions of HIV infection to atherosclerosis in the region.

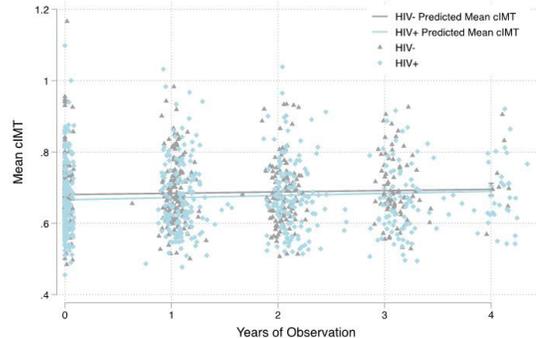
**Methods:** We conducted a prospective observational cohort study of PLWH on antiretroviral therapy (ART) over 40 years of age in rural Uganda, along with age- and sex-matched, population-based HIV-uninfected comparators. We collected data on CVD risk factors and carotid ultrasound measurements annually. We fitted linear mixed effects models, adjusted for CVD risk factors, to estimate the association between HIV serostatus and progression of carotid intima media thickness (cIMT). In stratified models, we estimated the contribution of HIV-specific indices on cIMT.

**Results:** We enrolled 155 PLWH and 154 HIV-uninfected individuals and collected 5,900 cIMT images during 1,045 visits, during a median of 4 annual visits per participant (IQR 3-4, range 1-5). Age (median 50.9 years) and sex (49% female) were similar by HIV serostatus, but PLWH had a lower systolic blood pressure compared to HIV-uninfected individuals (mean 113 vs 118, P<0.01), and were less likely to be current smokers (6 vs 21%, P<0.001), conferring a lower 10-year Framingham risk score (median 4.5 vs 6.1%, P=0.02). However,

PLWH had higher high sensitivity C-reactive protein (hsCRP) and soluble CD14 (sCD14) (P<0.001). At enrollment, PLWH had similar mean cIMT (0.665 versus 0.680 mm, P=0.15). In multivariable models, increasing age, blood pressure, and non-HDL cholesterol were associated with greater cIMT (P<0.05), however change in cIMT per year was similar by HIV serostatus (0.004 mm/year for HIV-negative [95% CI 0.001-0.007 mm], 0.006 mm/year for PLWH [95% CI 0.003-0.008 mm], HIV\*time interaction P=0.25). Model estimates were similar after adjustment for inflammatory markers. In models restricted to PLWH, use of a protease-inhibitor based regimen was associated with 0.042 greater cIMT (95%CI 0.002-0.082 mm, P=0.04).

**Conclusion:** In rural Uganda, treated HIV infection was not associated with faster cIMT progression. These results do not support classification of treated HIV infection as a risk factor for subclinical atherosclerosis progression in rural sub-Saharan Africa.

Figure 1. Scatter plot and model-adjusted estimates of mean carotid intima media thickness by HIV serostatus over four years of observation in Uganda



\*Estimates derived from a linear mixed effects model with carotid intima media thickness as outcome and the following predictors of interest: sex, age, diastolic blood pressure, hemoglobin A1c, non-HDL cholesterol, high-sensitivity C-reactive protein

#### 496 FACTORS ASSOCIATED WITH SYSTEMIC IMMUNE ACTIVATION IN A GLOBAL HIV COHORT

**Sara E. Looby**<sup>1</sup>, Amy Kantor<sup>2</sup>, Tricia H. Burdo<sup>3</sup>, Judith S. Currier<sup>4</sup>, Carl Fichtenbaum<sup>5</sup>, E. Turner Overton<sup>6</sup>, Judith A. Aberg<sup>7</sup>, Carlos Malvestutto<sup>8</sup>, Gerald S. Bloomfield<sup>9</sup>, Kathleen Fitch<sup>1</sup>, Pamela S. Douglas<sup>9</sup>, Steven Grinspoon<sup>1</sup>, Heather J. Ribaud<sup>2</sup>, Markella V. Zanni<sup>1</sup>, for the REPREVE Investigators

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Temple University, Philadelphia, PA, USA, <sup>4</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>5</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>6</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>7</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>8</sup>The Ohio State University, Columbus, OH, USA, <sup>9</sup>Duke University, Durham, NC, USA

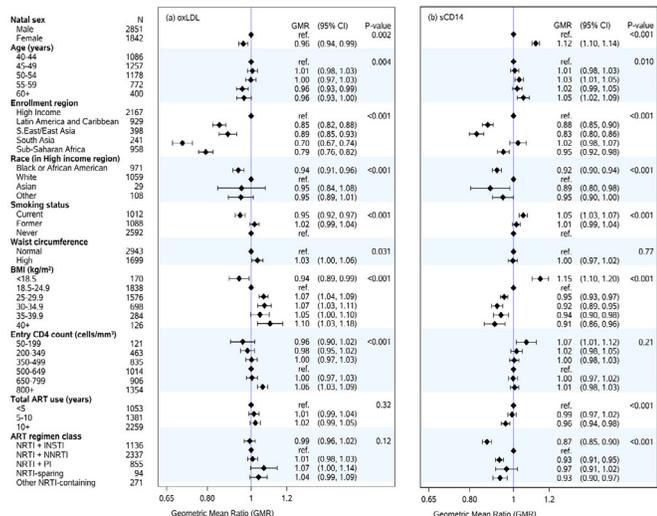
**Background:** Among antiretroviral therapy (ART)-treated people with HIV (PWH), persistent systemic immune activation may contribute to atherogenesis, cardiovascular disease (CVD) events, and mortality. Factors associated with key indices of systemic immune activation have not previously been characterized among a global cohort of PWH.

**Methods:** REPREVE (Randomized Trial to Prevent Vascular Events in HIV) enrolled ART-treated PWH age 40-75 with low-to-moderate traditional CVD risk. Among a subset of REPREVE participants, baseline levels of oxidized LDL cholesterol (oxLDL) and soluble CD14 (sCD14) were characterized by ELISA. Multivariable linear regression was used to examine levels of oxLDL and sCD14 by natal sex, geographic region, and age and to evaluate other participant characteristics associated with each marker.

**Results:** The cohort included 4694 participants from 5 Global Burden of Disease regions (39% female sex, 48% Black). Median (Q1, Q3) age was 50 (45, 54) years, body mass index (BMI) 26 (23, 30) kg/m<sup>2</sup>, LDL cholesterol 107 (87, 129) mg/dl, and CD4 count 634 (464, 842) cell/mm<sup>3</sup>; 48% had >10 years ART exposure. Median oxLDL and sCD14 for the cohort were 53 U/L (42, 68) and 1743 ng/mL (1469, 2064). Controlling for age and sex, oxLDL was highest in high-income regions and lowest in Sub-Saharan Africa and South Asia, while sCD14 was lowest in Latin America and S. East/East Asia. Aside from regional variation, male sex, younger age, white race (in high-income regions), and higher BMI and waist circumference were associated with higher oxLDL (Panel a). Female sex, older age, white race, current cigarette smoking, and lower BMI were associated with higher sCD14 (Panel b). Differences by current ART use were also apparent for sCD14. Findings were similar in sex-stratified analyses, analyses adjusted

for levels of LDL cholesterol (oxLDL only), and sensitivity analyses restricted to participants with undetectable HIV-1 RNA.

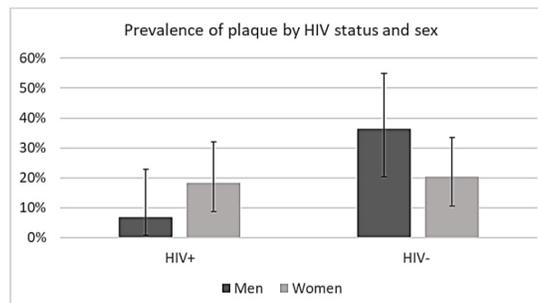
**Conclusion:** Factors associated with higher oxLDL and sCD14 – two key indices of immune-mediated CVD risk – differ. Male sex, residence in high-income regions, and higher BMI relate to higher oxLDL, while female sex, current cigarette smoking, and lower BMI relate to higher sCD14. Future studies may usefully elucidate ways in which medications and behavioral modifications (e.g. healthy diet, smoking cessation) influence oxLDL and sCD14 and whether dampening of these markers mediates CVD-protective effects.



Modeling was performed on log-transformed values, with results back-transformed for presentation as geometric mean ratios with 95% confidence intervals. Each panel represents a multivariable model, which also include adjustments for substance use and hypertension (estimates not shown).

vs. calcified plaque by HIV status. The prevalence of CAD differed substantially when stratified by sex and HIV status (Figure; HIV\*sex interaction p=0.019). Prevalent CAD positively correlated with classical monocytes (r=0.3, p=0.012) and negatively correlated with CX3CR1 expression (r=-0.31, p=0.011) in PLWH and negatively correlated with patrolling monocytes (r=-0.36, p=0.031) and tissue factor expression (r=-0.39, p=0.017) in PWOH.

**Conclusion:** Our results suggest that HIV may be associated more with progression rather than initiation of CAD in Uganda. Sex differences and unexpected inverse associations with monocyte activation markers merit further investigation.



Prevalence of coronary plaque among Ugandan men and women, stratified by HIV status. Error bars represent 95% confidence interval.

**497 SEX MODIFIES THE ASSOCIATION BETWEEN HIV AND CORONARY ARTERY DISEASE IN UGANDA**

**Milana Bogorodskaya**<sup>1</sup>, Seunghee Margevicius<sup>2</sup>, Cissy M. Kityo<sup>3</sup>, Rashidah Nazzinda<sup>3</sup>, Marcio S. Bittencourt<sup>4</sup>, Geoffrey Erem<sup>5</sup>, Sophie Nalukwago<sup>3</sup>, Moises A. Huaman<sup>6</sup>, Brian Ghoshhajra<sup>7</sup>, Mark Siedner<sup>7</sup>, Steven M. Juchnowski<sup>2</sup>, David A. Zidar<sup>8</sup>, Grace A. McComsey<sup>9</sup>, Chris T. Longenecker<sup>2</sup>

<sup>1</sup>MetroHealth Medical Center, Cleveland, OH, USA, <sup>2</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>3</sup>Joint Clinical Research Centre, Kampala, Uganda, <sup>4</sup>Universidade Federal de São Paulo, São Paulo, Brazil, <sup>5</sup>Makerere University, Kampala, Uganda, <sup>6</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>7</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>8</sup>Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA, <sup>9</sup>University Hospitals Cleveland Medical Center, Cleveland, OH, USA

**Background:** Little is known about the prevalence and risk factors for coronary artery disease (CAD) in sub-Saharan Africa, where the majority of people living with HIV (PLWH) live. We assessed the association of HIV with CAD severity and explored relationships with markers of monocyte activation in sex-stratified analyses of PLWH and people without HIV (PWOH) in Uganda.

**Methods:** The Ugandan Study of HIV effects on the Myocardium and Atherosclerosis (mUTIMA) follows 100 PLWH on antiretroviral therapy (ART) and 100 age- and sex-matched PWOH controls in Kampala, Uganda; all >45 years of age with >1 cardiovascular disease risk factor at study entry. At the year 2 exam (2017-2019), 189 participants had available coronary calcium (CAC) score and 165 had coronary CT angiography for this cross-sectional analysis. Common reasons for missing angiography data were tachycardia and poor renal function. A subset of participants (n=107) had both angiography and fresh whole blood flow cytometry for monocyte activation markers.

**Results:** Median age was 57.8 years and 63% were female. Overall, 88% had hypertension, 37% had diabetes, and 4% were current smokers. Global CAD risk was modestly higher for PWOH, but not statistically significant [median (IQR) 10-year ASCVD risk 7.2% (4.0-11.8) for PLWH vs. 8.6% (4.2-16.1) for PWOH, p=0.09]. Mean duration of ART was 12.7 years and 86% had HIV viral load <50c/ml. Despite prevalent risk factors, only 19% had CAC>0 and only 21% had any detectable coronary plaque overall, without unadjusted difference by HIV status. After adjustment for ASCVD risk score, HIV status was not associated with presence of any CAD (OR 0.55, 95% CI 0.23-1.30) but was associated with presence of more severe CAD (SSS>3) among those with any CAD (OR 10.9, 95% CI 1.67-70.45). There were no differences in distribution of non-calcified

**498 DIET QUALITY BY GLOBAL BURDEN OF DISEASE REGION IN PWH IN THE REPRIEVE TRIAL**

**Kathleen Fitch**<sup>1</sup>, Kristine Erlandson<sup>2</sup>, E. Turner Overton<sup>3</sup>, Sara McCallum<sup>1</sup>, Carl Fichtenbaum<sup>4</sup>, Judith A. Aberg<sup>5</sup>, Emma Kileel<sup>1</sup>, Laura Moran<sup>6</sup>, Anthony Holguin<sup>7</sup>, Markella V. Zanni<sup>1</sup>, Gerald S. Bloomfield<sup>8</sup>, Pamela S. Douglas<sup>9</sup>, Heather J. Ribaldo<sup>10</sup>, Steven Grinspoon<sup>1</sup>, for the REPRIEVE Investigators

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>3</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>4</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>5</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>6</sup>Social & Scientific Systems, Inc, Silver Spring, MD, USA, <sup>7</sup>Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, <sup>8</sup>Duke Global Health Institute, Durham, NC, USA, <sup>9</sup>Duke Clinical Research Institute, Durham, NC, USA, <sup>10</sup>Harvard TH Chan School of Public Health, Boston, MA, USA

**Background:** People with HIV (PWH) experience aging-associated comorbidities, including cardiovascular disease (CVD), at rates higher than the general population. Optimizing modifiable factors, such as diet, may delay onset or improve aging-associated comorbidities. However, diet quality across a global cohort of PWH has not been previously characterized.

**Methods:** REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) enrolled 7770 PWH, aged 40-75 years, at low-to-moderate traditional CVD risk, receiving ART. A cross-sectional analysis of the 7736 participants who completed the Rapid Eating Assessment for Participants (REAP) questionnaire at study entry was conducted. The overall REAP Score and scores for specific diet components were generated. Higher scores indicate better diet quality. Findings were summarized by Global Burden of Disease (GBD) super-region. Adjusted linear regression analyses were performed to examine differences in diet by key covariates.

**Results:** Among 7736 participants, median age was 50 years (Q1-Q3: 45-55), 31% were natal female, 43% were Black or African American, median BMI was 25.8 kg/m<sup>2</sup> (22.7-29.4), 48% has used ART for >10 years. Overall REAP Score was optimal in 13% of participants, but suboptimal or poor in 38% and 4% of participants, respectively. Participants residing in South Asia had the highest overall REAP Score, median 23 (21-25) (range 0-30), with 61% of participants' diet classified as optimal. Participants in South Asia consistently had the highest score for specific diet components (see Table). In the adjusted analysis, older age, less frequent alcohol use, and South East/East Asia and South Asia GBD regions were associated with higher REAP Score, while Black or African American race (in High Income and Sub-Saharan Africa GBD regions) were associated with lower REAP Score. In adjusted analyses restricted to each GBD region, older age (60+ years) was consistently associated with higher REAP Score, as was less frequent alcohol use, in all GBD regions except South East/East Asia.

**Conclusion:** Among PWH eligible for primary cardiovascular prevention, there were substantial variations in diet quality reported by GBD region. Diet was suboptimal or poor for 42% of trial participants. Important factors associated with poorer diet quality were age less than 60 years and more frequent alcohol use. Poor diet is an important, common modifiable risk factor which may be optimized to reduce CVD risk among PWH.

| Characteristic <sup>1</sup>                     | Global Burden of Disease Super Region |                      |                                    |                            |                    |                             |
|---|---------------------------------------|----------------------|------------------------------------|----------------------------|--------------------|-----------------------------|
|   | Total (N=7736)                        | High Income (N=4086) | Latin America & Caribbean (N=1421) | S. East/ East Asia (N=990) | South Asia (N=504) | Sub-Saharan Africa (N=1155) |
| Age (years)                                     | 50 (45-55)                            | 51 (46-55)           | 50 (44-55)                         | 47 (44-52)                 | 47 (44-52)         | 49 (44-54)                  |
| Natal sex female, n (%)                         | 2,413 (31%)                           | 872 (21%)            | 404 (28%)                          | 333 (56%)                  | 129 (26%)          | 675 (58%)                   |
| Race, n (%)                                     |                                       |                      |                                    |                            |                    |                             |
| Black or African American                       | 3,355 (43%)                           | 1,663 (41%)          | 537 (38%)                          | 0 (0%)                     | 0 (0%)             | 1,155 (100%)                |
| White   | 1,137 (15%)                           | 2,141 (53%)          | 546 (38%)                          | 2 (0%)                     | 0 (0%)             | 2 (0%)                      |
| Asian   | 555 (7%)                              | 43 (1%)              | 2 (0%)                             | 588 (100%)                 | 504 (100%)         | 0 (0%)                      |
| Other   | 1,919 (25%)                           | 1,276 (32%)          | 289 (20%)                          | 69 (12%)                   | 69 (14%)           | 214 (19%)                   |
| Smoking status (Current), n (%)                 | 5,777 (75%)                           | 2,949 (73%)          | 1,075 (76%)                        | 431 (73%)                  | 478 (95%)          | 844 (73%)                   |
| Alcohol use (Rarely/never), n (%)               | 5 (2-7)                               | 5 (3-8)              | 4 (3-7)                            | 2 (1-4)                    | 3 (1-5)            | 4 (1-7)                     |
| ASCVD risk score (%)                            | 25.8 (22.7-29.4)                      | 26.8 (23.8-30.6)     | 25.8 (23.3-28.6)                   | 22.7 (20.5-25.0)           | 22.9 (20.5-25.9)   | 24.7 (21.2-29.6)            |
| BMI (kg/m <sup>2</sup> )                        | 3.740 (48%)                           | 2.289 (56%)          | 470 (33%)                          | 412 (70%)                  | 156 (31%)          | 413 (36%)                   |
| CD4 count >500 cells/mm <sup>3</sup> , n (%)    | 5,239 (68%)                           | 2,739 (67%)          | 1,021 (72%)                        | 422 (72%)                  | 313 (62%)          | 744 (64%)                   |
| Overall REAP Score <sup>2</sup> (max score: 30) | 17 (13-20)                            | 16 (12-20)           | 17 (14-20)                         | 16 (16-21)                 | 23 (21-25)         | 15 (12-18)                  |
| Optimal (range 22.5-30)                         | 1,020 (13%)                           | 447 (11%)            | 119 (8%)                           | 70 (12%)                   | 309 (61%)          | 75 (6%)                     |
| Good (range >15- <22.5)                         | 3,488 (45%)                           | 1,718 (42%)          | 770 (54%)                          | 379 (64%)                  | 178 (35%)          | 443 (38%)                   |
| Suboptimal (range >7.5- <15)                    | 2,841 (36%)                           | 1,686 (42%)          | 516 (36%)                          | 139 (24%)                  | 17 (3%)            | 573 (50%)                   |
| Poor (range 0- <7.5)                            | 287 (4%)                              | 204 (5%)             | 16 (1%)                            | 2 (0%)                     | 0 (0%)             | 65 (6%)                     |
| Saturated fat (max score: 16)                   | 10 (7-12)                             | 9 (7-11)             | 10 (8-12)                          | 11 (10-13)                 | 15 (13-16)         | 9 (7-12)                    |
| Fiber (max score: 6)                            | 3 (1-4)                               | 3 (2-4)              | 2 (1-4)                            | 3 (2-4)                    | 4 (3-4)            | 2 (1-5)                     |
| Sodium (max score: 6)                           | 5 (4-6)                               | 5 (4-6)              | 5 (4-6)                            | 5 (4-6)                    | 5 (4-6)            | 5 (4-6)                     |

<sup>1</sup>Data are presented as median (IQR) unless otherwise specified.  
<sup>2</sup>Higher REAP score and component score (saturated fat, fiber, sodium) indicates more optimal diet.  
 Abbreviations: ASCVD, atherosclerotic cardiovascular disease score; BMI, body mass index; ART, antiretroviral therapy; REAP, rapid eating assessment for participants.

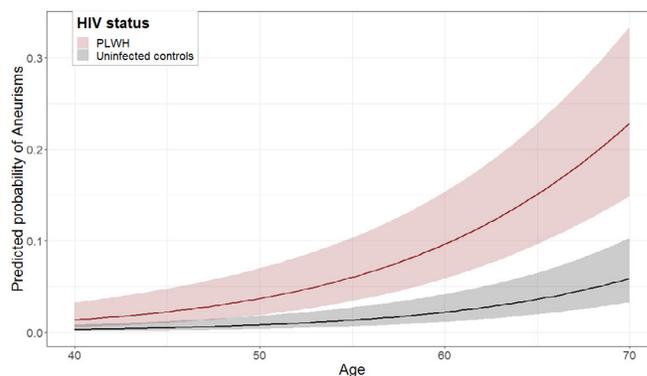


Figure 1. Predicted probability of aortic aneurysms in uninfected controls and people living with HIV (PLWH). Predicted probability was calculated using a logistic regression model that included HIV, age, BMI = 25, sex = "Male", Origin = "Scandinavian or other European", Smoking status = "Ex smoker", Hypertension = "Yes", Hyperlipidemia = "No". Abbreviation: HIV, human immunodeficiency virus.

## 499 HIV INFECTION IS INDEPENDENTLY ASSOCIATED WITH AORTIC ANEURYSMS

**Julie Høgh<sup>1</sup>**, Michael H. Pham<sup>1</sup>, Andreas D. Knudsen<sup>1</sup>, Rebekka F. Thudium<sup>1</sup>, Marco Gelpi<sup>1</sup>, Per E. Sigvardsen<sup>1</sup>, Andreas E. Fuchs<sup>1</sup>, Jørgen T. Kuhl<sup>1</sup>, Shoaib Afzal<sup>2</sup>, Børge Nordestgaard<sup>2</sup>, Thomas Benfield<sup>3</sup>, Lars Køber<sup>1</sup>, Jan Gerstorff<sup>1</sup>, Klaus F. Kofoed<sup>1</sup>, Susanne D. Nielsen<sup>1</sup>

<sup>1</sup>Rigshospitalet, Copenhagen, Denmark, <sup>2</sup>Herlev and Gentofte Hospital, Copenhagen, Denmark, <sup>3</sup>Hvidovre Hospital, Hvidovre, Denmark

**Background:** Increased risk of cardiovascular disease has been reported in people living with HIV (PLWH). Little is known about the prevalence of aortic aneurysms among PLWH compared to uninfected individuals. Here we investigate if HIV status is independently associated with having aortic aneurysms. Furthermore, we determine risk factors associated with aortic aneurysms in PLWH.

**Methods:** PLWH aged 40 years or older were recruited from the Copenhagen Comorbidity in HIV Infection (COCOMO) study and matched on age and sex with uninfected controls from the Copenhagen General Population Study. Aortic dimensions were assessed using contrast enhanced CT images. Aortic aneurysms were defined according to the European Society of Cardiology; i.e. an aortic dilation at least 50% larger in diameter compared to the expected normal diameter or an infrarenal aortic diameter  $\geq 30$  mm.

**Results:** We included 594 PLWH and 1188 uninfected controls, of which 88% and 90% were male and median (IQR) age was 52 (47-60) and 52 (48-61) years, respectively. We found 46 aneurysms in 42 (7%) of PLWH and 31 aneurysms in 29 (2.4%) of the uninfected controls ( $p < 0.001$ ). PLWH had a significantly higher prevalence of ascending, suprarenal and infrarenal aortic aneurysms, but not of descending aortic aneurysms, than the controls. After adjusting for age, sex, hypertension, smoking status, BMI, hyperlipidemia and country of origin, HIV was independently associated with aortic aneurysms (adjusted odds ratio: 4.50 [95%CI: 2.54-7.99],  $p < 0.001$ ). Within PLWH, obesity and hepatitis B coinfection were associated with higher odds of aortic aneurysms, whereas other risk factors, including syphilis and antiretroviral therapy, were not. Predicted probability of aortic aneurysms in PLWH and uninfected controls according to age is shown in Figure 1 ( $p$  interaction 0.510).

**Conclusion:** PLWH had increased odds of aortic aneurysms compared to uninfected controls. HIV was independently associated with a fourfold higher odds of aortic aneurysms. Our findings suggest that increased attention of aortic aneurysms in PLWH is warranted, and further studies should be conducted to determine if screening for aortic aneurysms in PLWH is beneficial.

## 500 HIV-1, INSUFFICIENT SLEEP, AND ENDOTHELIAL VASODILATOR FUNCTION

**Kelly A. Stockelman<sup>1</sup>**, Anthony R. Bain<sup>2</sup>, Cindy S. Firnhaber<sup>3</sup>, Jared J. Greiner<sup>1</sup>, Brian L. Stauffer<sup>3</sup>, Elizabeth Connick<sup>4</sup>, Christopher A. DeSouza<sup>1</sup>

<sup>1</sup>University of Colorado Boulder, Boulder, CO, USA, <sup>2</sup>University of Windsor, Windsor, Ontario, Canada, <sup>3</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>4</sup>University of Arizona, Tucson, AZ, USA

**Background:** The increased risk and incidence of cardiovascular disease (CVD) in adults living with HIV-1 is not solely due to worsening of traditional CVD risk factors, but also involves ill-defined factors related to the virus and/or its therapies. More than 70% of adults living with HIV-1 report sleep problems, the most common malady being short nightly sleep duration (<7 h/night). Short nightly sleep duration is associated with increased CVD risk and events. An underlying mechanism for the sleep-related increase in CVD is a profound worsening in vascular endothelial function. The influence of insufficient sleep on vascular endothelial function in HIV-1-seropositive adults is unknown. We tested the hypotheses that: 1) short nightly sleep duration is associated with lower nitric oxide (NO)-mediated endothelium-dependent vasodilation in antiretroviral (ART)-treated adults living with HIV-1; and 2) the short sleep-related reduction in endothelial vasodilator function is due, at least in part, to increased oxidative stress.

**Methods:** Thirty-two sedentary, middle-aged HIV-1-seropositive adults on stable antiretroviral therapy were studied: 16 with normal nightly sleep duration (12M/4F; age:  $50 \pm 2$  yr; BMI:  $25.4 \pm 0.7$  kg/m<sup>2</sup>; sleep:  $7.8 \pm 0.3$  h/night) and 16 with short nightly sleep duration (14M/2F;  $51 \pm 2$  yr;  $25.4 \pm 0.8$  kg/m<sup>2</sup>;  $5.6 \pm 0.3$  h/night). Forearm blood flow (FBF) responses to intra-arterial infusion of acetylcholine (ACh), in the absence and presence of the endothelial NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA) and the antioxidant vitamin C were determined by venous occlusion plethysmography.

**Results:** FBF responses to ACh were significantly lower (~20%) in the short sleep (from  $4.5 \pm 0.3$  to  $12.4 \pm 0.6$  mL/100 mL tissue/min) vs normal sleep adults (from  $4.7 \pm 0.3$  to  $14.5 \pm 0.7$  mL/100 mL tissue/min). L-NMMA significantly reduced (~15%) the FBF response to ACh in the normal sleep but not the short sleep group; whereas, vitamin C significantly increased (~30%) the vasodilator response to ACh in short sleep but not the normal sleep group.

**Conclusion:** Habitual short sleep duration is associated with lower endothelium-dependent vasodilation in adults living with HIV-1 due, in part, to increased oxidative stress. Reduced NO-mediated endothelium-dependent vasodilation may increase the CVD risk in adults living with HIV-1 who sleep < 7h/night.

## 501 HEROIN USE IS ASSOCIATED WITH HIGH-AORTIC BUT LOW-SPLEEN/MARROW UPTAKE BY PET IN HIV

**Corryllyn O. Hileman<sup>1</sup>**, Scott E. Janus<sup>2</sup>, Jared C. Durieux<sup>2</sup>, Claire Sullivan<sup>2</sup>, Ann K. Avery<sup>1</sup>, Danielle Labbato<sup>2</sup>, Cheryl Smith<sup>1</sup>, Grace A. McComsey<sup>2</sup>

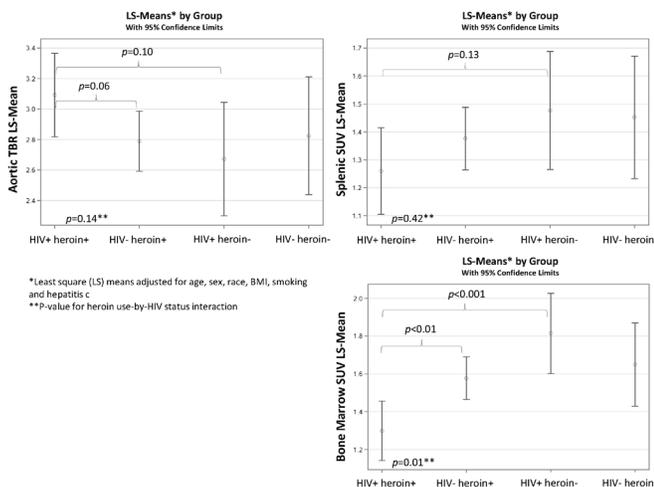
<sup>1</sup>MetroHealth Medical Center, Cleveland, OH, USA, <sup>2</sup>University Hospitals Cleveland Medical Center, Cleveland, OH, USA

**Background:** Heroin use may work synergistically with HIV infection to cause greater immune dysregulation than either factor alone. Unraveling how this affects end organ disease is key as it may play a role in the excess mortality seen in people with HIV who use heroin even despite access to care and antiretroviral therapy.

**Methods:** In this prospective, cross-sectional study, adults with and without HIV who use and do not use heroin underwent FDG-PET to compare tissue specific inflammation, aortic (target-to-background ratio or TBR), splenic and bone marrow (standardized uptake value or SUV). Least squares regression was utilized to compare means between 1) HIV+ heroin+ vs HIV+ heroin-, 2) HIV- heroin+ vs HIV- heroin-, and 3) HIV+ heroin+ vs HIV- heroin+ and test for effect modification (heroin use-by-HIV status interaction).

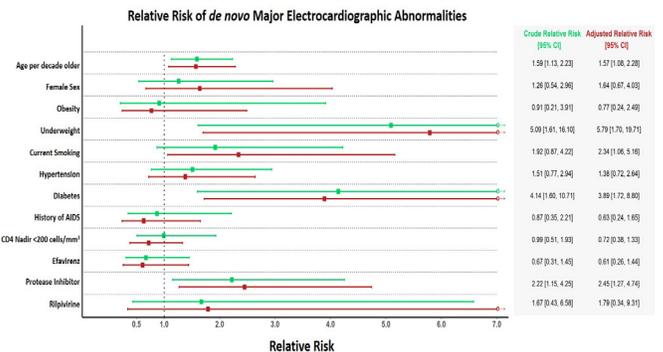
**Results:** 110 participants enrolled (23 HIV+ heroin+, 51 HIV- heroin+, 20 HIV+ heroin-, 16 HIV- heroin-). Median (IQR) age was 41 (33, 51) yrs; 74% were men. Heroin+ were more likely Hispanic regardless of race (23 vs 6%), smokers (99 vs 44%) and to have active hepatitis C (57 vs 0%) (p<0.01 for all). Among HIV+, heroin users had lower current (591 vs 790 cells/mm<sup>3</sup>), but similar nadir CD4 counts (247 cells/mm<sup>3</sup>), HIV duration (12 yrs) and proportion with HIV-1 RNA <200 copies/mL (91%). Aortic TBR was 0.41 higher in HIV+ heroin+ than HIV+ heroin- (p=0.03) and 0.26 higher than HIV- heroin+ (p=0.09) which attenuated slightly with adjustment, but were still apparent (Figure). The effect of heroin use on splenic and bone marrow SUV was opposite. Splenic (bone marrow) SUV was 0.21 (0.43) lower in HIV+ heroin+ than HIV+ heroin- (p=0.05 for spleen and p<0.001 for bone marrow) and 0.13 (0.33) lower than HIV- heroin+ (p=0.13 and p<0.0001). The differences attenuated for splenic SUV with adjustment, but remained significant for bone marrow SUV. Additionally, HIV status modified the effect of heroin use on bone marrow SUV (Figure).

**Conclusion:** Aortic inflammation was greatest in HIV+ heroin+, but paradoxically bone marrow and splenic (trend) activity was the least in this group suggesting complex and possibly divergent pathophysiology within these different end organs.



**Results:** Of 667 PLWH (85% men) without major ECG abnormalities at baseline, 34 (5%) developed de novo major ECG abnormalities after a median of 2.3 years. At baseline, the mean age was 51, 26% were current smokers, 2% used methadone, and 29% and 31% used protease inhibitors or efavirenz, respectively. After adjustment, age (RR: 1.57 [1.08-2.28] per decade older), being underweight (RR: 5.79 [1.70-19.71]), current smoking (RR: 2.34 [1.06-5.16]), diabetes (RR: 3.89 [1.72-8.80]) and protease inhibitor use (RR: 2.45 [1.27-4.74]) were associated with higher risk of de novo major ECG abnormalities. Of PLWH without prolonged QTc at baseline, 11 (1.6%) participants developed de novo prolonged QTc. Efavirenz use was associated with 4.4 [0.9, 7.9] ms increased lengthening of QTc between baseline and follow-up. Efavirenz use was not associated with a statistically significant higher risk of de novo prolonged QTc (adjusted RR: 3.01 [0.87-10.40], p=.082).

**Conclusion:** Five percent of well-treated PLWH acquired de novo major ECG abnormalities after 2.3 years of follow-up, and protease inhibitor use was associated with more than twice the risk of de novo major ECG abnormalities. Although efavirenz was associated with longer QTc intervals, the absolute difference was small, and efavirenz was not significantly associated with higher risk of prolonged QTc after adjustment.



**502 DE NOVO ELECTROCARDIOGRAPHIC ABNORMALITIES IN WELL-TREATED PERSONS WITH HIV**

**Andreas D. Knudsen<sup>1</sup>**, Claus Graff<sup>2</sup>, Jonas B. Nielsen<sup>1</sup>, Magda T. Thomsen<sup>1</sup>, Thomas Benfield<sup>3</sup>, Jan Gerstoft<sup>1</sup>, Lars Køber<sup>1</sup>, Julie Høgh<sup>1</sup>, Klaus F. Kofoed<sup>1</sup>, Susanne D. Nielsen<sup>1</sup>

<sup>1</sup>Rigshospitalet, Copenhagen, Denmark, <sup>2</sup>Aalborg University Hospital, Aalborg, Denmark, <sup>3</sup>Hvidovre Hospital, Hvidovre, Denmark

**Background:** Persons living with HIV (PLWH) may have increased incidence of cardiovascular events and longer QTc intervals than uninfected persons.

We aimed to investigate the incidence and risk factors of de novo major electrocardiogram (ECG) abnormalities and QTc prolongation in PLWH.

**Methods:** We included virologically suppressed PLWH without major ECG abnormalities, who attended the 2-year follow-up in the Copenhagen comorbidity in HIV infection (COCOMO) study. At baseline and follow-up, participants had similar assessments, including physical exams, ECG, and questionnaires on lifestyle, and smoking behaviour. We obtained data on HIV treatment and use of methadone through review of medical records. ECGs were categorized according to The Minnesota Code Manual of Electrocardiographic Findings. De novo major ECG abnormalities were defined as new major Minnesota Code Manual abnormalities. QT interval was corrected according to Bazett's formula and prolonged QTc was defined as QTc > 460ms in females and QTc > 450ms in males.

**503 WEIGHT GAIN AFTER SWITCHING DIFFERENT INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)**

**Grace A. McComsey<sup>1</sup>**, Paul Sax<sup>2</sup>, Keri N. Althoff<sup>3</sup>, Todd Brown<sup>4</sup>, Janna Radtchenko<sup>5</sup>, Helena Diaz-Cuervo<sup>6</sup>, Joshua Gruber<sup>7</sup>, Moti Ramgopal<sup>8</sup>, Steven Santiago<sup>9</sup>, Graeme Moyle<sup>10</sup>, Karam Mounzer<sup>11</sup>, Richard Elion<sup>5</sup>

<sup>1</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>2</sup>Harvard Medical School, Boston, MA, USA, <sup>3</sup>Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA, <sup>4</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>5</sup>Trio Health, Louisville, CO, USA, <sup>6</sup>Gilead Sciences, Madrid, Spain, <sup>7</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>8</sup>Midway Immunology and Research Center, Fort Pierce, FL, USA, <sup>9</sup>Care Resource, Miami, FL, USA, <sup>10</sup>Chelsea and Westminster Hospital, London, UK, <sup>11</sup>Philadelphia FIGHT, Philadelphia, PA, USA

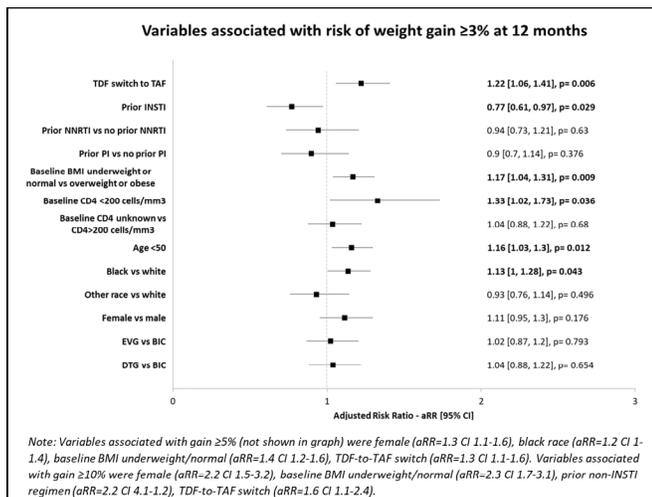
**Background:** INSTIs are components of all recommended initial regimens. They have been associated with weight gain both in clinical trials and observational studies. TDF/FTC treatment has been associated with less weight gain than other NRTI pairs. Little is known about how individual INSTIs contribute to weight gain in real-world clinical practice while accounting for TDF-to-TAF switch or prior TDF.

**Methods:** The Trio Health HIV database was used in this retrospective study. Eligible patients (pts) were ≥18 yrs, suppressed at baseline (BL) and during study period (12 mo), switched to a new INSTI regimen (Jan'15-Jun'19), with weight measurements at BL and 12 (±3) mo. Univariate analyses [UV] were conducted using chi-square and t-test. Multivariable analyses (MV) using binary outcomes of gain ≥3, 5, and 10% (BL to 12 mo) were conducted using log binomial models adjusting for age, gender, race, BL BMI and CD4, pre-switch and post-switch drug class, individual INSTI (DTG, EVG, BIC), and TDF-to-TAF switch (sensitivity: pre-switch TDF).

**Results:** Of 2272 pts, 39% were prescribed EVG, 31% BIC, 28% DTG, 2% RAL (RAL excluded from MV). Of eligible pts, 64% received prior INSTI, 57% prior TDF; 47% switched from TDF to TAF. Pts differed in BL characteristics (p<.05): <50 years (EVG 56% vs 46% DTG); white (BIC 60% vs DTG 48%); black (DTG 40% vs EVG 30%, BIC 24%); female (12% EVG, 11% BIC vs 18% DTG, 27% RAL); CD4 <200 cells/mm<sup>3</sup> (1% EVG, 2% BIC vs 6% DTG, 4% RAL). Pts had mean BL weight 84 kg (SD 17.6) and gained mean 1.3 kg (5.9): EVG 1.5 (5.4), BIC 0.9 (5.6), DTG 1.2 (6.5), RAL 1.9 (9.4). In UV, 41% of EVG pts vs 35% BIC gained ≥3%, p=0.015; 10% of

DTG vs 6% of BIC pts gained  $\geq 10\%$ ,  $p=0.046$ . There were no differences in gain by InSTI after controlling for BL characteristics, prior and current drug class, and TDF-to-TAF switch vs no TDF-to-TAF switch at all gain thresholds; TDF-to-TAF switchers were more likely to gain weight vs non TDF-to-TAF switch [Figure]. In sensitivity analysis accounting for pre-switch TDF (vs no TDF) there were also no differences in gain by InSTI type. Pts with prior TDF were more likely to gain  $\geq 3\%$  (aRR=1.2 CI 1-1.4) and  $\geq 5\%$  (aRR=1.4 CI 1.1-1.7) but not  $\geq 10\%$  (aRR=1.5 CI 0.9-2.4).

**Conclusion:** After accounting for pt characteristics and TDF-to-TAF switch or pre-switch TDF, there was no difference in weight gain  $\geq 3, 5, 10\%$  among different InSTIs. Future studies evaluating the effect of different InSTIs on weight gain should control for NRTI switches and demographics.



**504 WEIGHT GAIN AMONG PWH WHO SWITCH TO ART-CONTAINING InSTIs OR TAF**

**Frank Palella**<sup>1</sup>, Qingjiang Hou<sup>2</sup>, Jun Li<sup>3</sup>, Jonathan Mahnken<sup>4</sup>, Kimberly J. Carlson<sup>2</sup>, Marcus Durham<sup>5</sup>, Douglas Ward<sup>6</sup>, Jack Fuhrer<sup>7</sup>, Ellen M. Tedaldi<sup>7</sup>, Richard Novak<sup>8</sup>, Kate Buchacz<sup>3</sup>

<sup>1</sup>Northwestern University, Chicago, IL, USA, <sup>2</sup>Cerner Corporation, Kansas City, MO, USA, <sup>3</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>4</sup>University of Kansas Medical Center, Kansas City, KS, USA, <sup>5</sup>Dupont Circle Physicians Group, Washington, DC, USA, <sup>6</sup>Stony Brook University, Stony Brook, NY, USA, <sup>7</sup>Temple University, Philadelphia, PA, USA, <sup>8</sup>University of Illinois at Chicago, Chicago, IL, USA

**Background:** ART-associated weight changes among persons with HIV (PWH) whose first InSTI exposure is via an ART switch regimen require further long-term study in routine HIV care.

**Methods:** We analyzed 2007-2018 medical records data of patients who were InSTI-naïve and virally suppressed (VS) for  $\geq 1$  year on non-InSTI-based ART, switched ART and remained VS. Patients were prescribed InSTI- or non-InSTI-based ART for  $\geq 6$  months, had  $\geq 2$  body mass index (BMI) values in the year before switch and  $\geq 1$  after. We analyzed weight change (BMI, presuming height was stable) before and after switch using generalized linear mixed effects models (GLMM), and estimated relative contribution of InSTI- and TAF-containing ART to BMI gain by contrasting GLMM-estimated slopes.

**Results:** Among 736 persons (with 5,316 person-years of observation), 441 (60%) switched to InSTI-based ART. Proximal to time of switch, both groups (InSTI vs non-InSTI) had similar CD4 cell count (634 vs. 626 cells/ $\mu$ L,  $P=0.85$ ) and median BMI (23.0 vs. 24.0 kg/m<sup>2</sup>,  $P=0.62$ ). Of InSTI-based ART regimens, 236 (54%) included raltegravir, 112 (25%) elvitegravir, and 143 (32%) dolutegravir. In GLMM, monthly rate of BMI increases post-switch was faster for InSTI-based than non-InSTI based ART (rate difference  $\pm$  stdev: 0.0525  $\pm$  0.006,  $p<0.001$ ) [0.041, 0.064 95% CI]. There was an inflection point for BMI changes at 8 months post switch and the slopes were similar according to TAF use (Table 1). Among persons receiving InSTI-based ART with TAF, during the first 8 months 87% of weight gain (BMI change) was associated with InSTI and 13% with TAF; after 8 months post-ART switch, these estimated contributions were 27% and 73%, respectively. For non-InSTI TAF-based ART, 84% of weight gain was associated with TAF both during and after the first 8 months post switch. Older age and higher baseline BMI but not sex or race/ethnicity were associated with more

rapid weight gain. BMI changes were not statistically different post-switch by type of InSTI.

**Conclusion:** Among VS persons who switched ART, both InSTI and TAF use were independently associated with weight gain. During the first 8 months post-switch, the rate of weight gain was greatest and mostly associated with InSTI use; after that, continued gradual weight gain was mostly associated with TAF use. These data help define the individual contribution, magnitude, and duration of effect upon weight gain of InSTI and TAF use.

**Table 1.** Rate of monthly change in BMI (kg/m<sup>2</sup>) and associated 95% confidence intervals, according to treatment group, IIV Outpatient Study, 2007-2018, N=736.

| Group/Stratum after switch* | Trajectory 0-8 months after switch | Trajectory 8+ months after switch | Trajectory before switch | Difference (before switch vs 0-8 months after switch) | Difference (before switch vs 8+ months after switch) |
|-----------------------------|------------------------------------|-----------------------------------|--------------------------|---|--|
| InSTI with TAF (n = 188)    | 0.062 (0.049, 0.075)               | 0.011 (0.001, 0.02)               | 0.000 (0.000, 0.001)     | 0.061 (0.048, 0.074)                                  | 0.010 (0.001, 0.0200)                                |
| InSTI without TAF (n = 253) | 0.054 (0.043, 0.07)                | 0.003 (0.000, 0.006)              | 0.000 (0.000, 0.001)     | 0.054 (0.042, 0.065)                                  | 0.003 (-0.001, 0.006)                                |
| Non InSTI TAF (n = 128)     | 0.010 (0.001, 0.019)               | 0.011 (0.002, 0.02)               | 0.007 (0.006, 0.008)     | 0.007 (0.006, 0.008)                                  | 0.007 (0.006, 0.009) **                              |
| Non-InSTI non TAF (n = 167) | 0.002 (0.000, 0.004)               | 0.002 (0.000, 0.004)              | 0.007 (0.006, 0.008)     | -0.005 (-0.006, -0.002)                               | -0.005 (-0.008, -0.002)                              |

\*Models adjusted for age, sex, race/ethnicity, and BMI measured at time of treatment switch. N's show number of unique persons contributing data to each of the estimates; \*\*Fully based on model estimated trajectory since no patients in the study cohort had been on non-InSTI and TAF for more than 8 months.

**505 WEIGHT AND LIPID CHANGES IN PHASE 3 CABOTEGRAVIR AND RILPIVIRINE LONG-ACTING TRIALS**

**Parul Patel**<sup>1</sup>, Ronald D'Amico<sup>1</sup>, Shanker Thiagarajah<sup>2</sup>, Sterling Wu<sup>3</sup>, Emilie Elliot<sup>4</sup>, Joseph W. Polli<sup>1</sup>, Ojesh Upadhyay<sup>3</sup>, Rodica Van Solingen-Ristea<sup>5</sup>, Chloe Orkin<sup>6</sup>, E. Turner Overton<sup>7</sup>, Susan Swindells<sup>8</sup>, Jean A. Van Wyk<sup>9</sup>, Matthew Bosse<sup>1</sup>, Vani Vannappagari<sup>1</sup>

<sup>1</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>2</sup>GlaxoSmithKline, Uxbridge, UK, <sup>3</sup>GlaxoSmithKline, Collegeville, PA, USA, <sup>4</sup>ViiV Healthcare, Madrid, Spain, <sup>5</sup>Janssen Research and Development, Beerse, Belgium, <sup>6</sup>Queen Mary University of London, London, UK, <sup>7</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>8</sup>University of Nebraska Medical Center, Omaha, NE, USA, <sup>9</sup>ViiV Healthcare, Brentford, UK

**Background:** Weight gain and metabolic alterations have been reported with integrase strand transfer inhibitor (InSTI)-based antiretroviral (ARV) regimens. Long-acting (LA) cabotegravir (CAB), an InSTI, and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor, constitute a highly effective 2-drug regimen administered intramuscularly monthly or every 2 months for the maintenance of virologic suppression. Weight and lipid changes over 48 weeks in adults with virologic suppression receiving CAB+RPV LA in Phase 3/3b clinical trials are presented.

**Methods:** Data in participants naïve to CAB+RPV LA and randomized to CAB+RPV LA every 4 weeks (Q4W), every 8 weeks (Q8W), or oral comparator ARV therapy (CAR) through 48 weeks were pooled from the ATLAS, FLAIR, and ATLAS-2M studies. Demographics and baseline characteristics were collected for each group and changes in weight, BMI, and lipids from baseline to Week 48 were analyzed.

**Results:** Participants' baseline characteristics are summarized in Table 1. Median (range) change in weight from baseline to Week 48 was 1.20 kg (-27.5, 40.9) in Q4W, 1.25 kg (-16.0, 22.2) in Q8W, and 1.00 kg (-28.0, 39.0) in the CAR groups.  $\geq 10\%$  weight increase occurred in 77 (8%) participants in Q4W, 15 (5%) in Q8W, and 39 (7%) in the CAR groups. Median (range) change in BMI was 0.40 kg/m<sup>2</sup> (-9.9, 14.3) in Q4W, 0.42 kg/m<sup>2</sup> (-4.8, 7.3) in Q8W, and 0.35 kg/m<sup>2</sup> (-8.2, 13.7) in the CAR groups. 13.4% (59/440) of participants in Q4W, 14.6% (22/151) in Q8W, and 13.8% (41/298) in the CAR groups underwent an upward shift in BMI category from normal, resulting in 3.9% (30/766, Q4W), 4.1% (11/268, Q8W), and 4.7% (23/487, CAR) of participants developing clinical obesity (BMI >30 kg/m<sup>2</sup>). There were no clinically significant changes in triglycerides; total, HDL, and LDL cholesterol; and TC/HDL ratios among the 3 treatment groups.

**Conclusion:** In this pooled analysis, changes in weight and lipid parameters over 48 weeks were modest and similar, respectively, in participants receiving CAB+RPV LA Q4W or Q8W compared to CAR. Since InSTI-associated weight changes have only recently emerged, collection of weight data across the CAB development program was not standardized at sites and limited metabolic data were collected. Future and on-going studies will further characterize potential InSTI-associated weight gain and metabolic perturbations.

**Table 1: Baseline Characteristics of ATLAS, FLAIR, and ATLAS-2M Participants**

| Baseline demographics/characteristics (ITT-E pop) | Pooled Q4W arm ATLAS, FLAIR, ATLAS-2M (n=918) | Q8W arm ATLAS-2M (n=327) | Pooled CAR arm ATLAS AND FLAIR <sup>1</sup> (n=591) |
|---|---|--------------------------|---|
| Median age (range), years                         | 39 (19-74)                                    | 41 (20-83)               | 38 (18-82)  |
| % Female (sex at birth)                           | 26%   | 22%                      | 28%   |
| Ethnicity % White                                 | 75%   | 73%                      | 69%   |
| BL median CD4 count (cells/mm <sup>3</sup> )      | 661   | 643                      | 641   |
| BL median weight (range), kg                      | 76.0 (41.2-139.4)                             | 77.00 (49.0-136.9)       | 75.2 (36.0-162.8)                                   |
| BMI category                                      |   |                          |   |
| • Underweight (<18.5 kg/m <sup>2</sup> )          | 20 (2%)                                       | 4 (1%)                   | 12 (2%)   |
| • Normal (18.5-25 kg/m <sup>2</sup> )             | 440 (48%)                                     | 151 (46%)                | 298 (50%)   |
| • Overweight (25-30 kg/m <sup>2</sup> )           | 306 (33%)                                     | 113 (35%)                | 178 (30%)   |
| • Obese (>30 kg/m <sup>2</sup> )                  | 152 (17%)                                     | 59 (18%)                 | 103 (17%)   |
| BL lipids, mean (SD)                              |   |                          |   |
| TG (mmol/L)                                       | 1.43 (1.014)                                  | 1.46 (0.954)             | 1.43 (1.051)  |
| TC (mmol/L)                                       | 4.73 (1.014)                                  | 4.82 (1.052)             | 4.72 (1.055)  |
| LDL (mmol/L)                                      | 2.74 (0.855)                                  | 2.78 (0.899)             | 2.71 (0.835)  |
| HDL (mmol/L)                                      | 1.34 (0.414)                                  | 1.39 (0.421)             | 1.36 (0.428)  |
| TC:HDL ratio                                      | 3.82 (1.538)                                  | 3.73 (1.276)             | 3.72 (1.197)  |
| Medical history (%)                               |   |                          |   |
| • Hypertension                                    | 92 (10%)                                      | 51 (16%)                 | 76 (13%)  |
| • Diabetes  | 22 (2%)                                       | 11 (3%)                  | 22 (4%)   |
| Select co-medications (%)                         |   |                          |   |
| • Antihypertensives                               | 11 (1.2%)                                     | 6 (1.8%)                 | 3 (0.5%)  |
| • Anti-diabetes                                   | 16 (1.7%)                                     | 10 (3.1%)                | 17 (2.9%)   |
| • Anti-lipids                                     | 90 (9.8%)                                     | 39 (11.9%)               | 30 (5.1%)   |
| • SSRIs   | 54 (5.9%)                                     | 14 (4.3%)                | 28 (4.7%)   |
| • Antipsychotics                                  | 13 (1.4%)                                     | 9 (2.8%)                 | 7 (1.2%)  |
| Pre-switch ART regimen (%)                        |   |                          |   |
| • INI-based                                       | 526 (57%)                                     | 136 (42%)                | 382 (65%)   |
| • PI-based  | 81 (9%)                                       | 40 (12%)                 | 54 (9%)   |
| • NNRTI-based                                     | 311 (34%)                                     | 151 (46%)                | 155 (26%)   |

<sup>1</sup>FLAIR study baseline was at Week 20, at which DTG/ABC/3TC or DTG+TDF/3TC was switched to CAB+RPV/LA.

| Outcome   | Overall (n=4498)            |         | Natal Sex=Female (n=1039)   |         | Natal Sex=Male (n=3459)     |         |
|---|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|
|   | Parameter Estimate (95% CI) | P-value | Parameter Estimate (95% CI) | P-value | Parameter Estimate (95% CI) | P-value |
| <b>Primary analyses: linear regressions</b>   |                             |         |                             |         |                             |         |
| BMI (kg/m <sup>2</sup> )  | 1.6 (1.2, 1.9)              | <0.0001 | 2.5 (1.4, 3.5)              | <0.0001 | 1.1 (0.8, 1.5)              | <0.0001 |
| Waist circumference (cm)  | 3.7 (2.8, 4.6)              | <0.0001 | 5.0 (2.8, 7.3)              | <0.0001 | 2.8 (1.8, 3.8)              | <0.0001 |
| Fasting glucose (mg/dL)   | 0.02 (-0.9, 0.9)            | 0.97    | 0.5 (-1.5, 2.4)             | 0.64    | -0.2 (-1.2, 0.8)            | 0.75    |
| Fasting LDL (mg/dL)   | -0.2 (-2.1, 1.8)            | 0.87    | 0.2 (-4.1, 4.6)             | 0.91    | -0.7 (-2.9, 1.5)            | 0.54    |
| <b>Secondary Analyses: quantile regressions (75<sup>th</sup> quantile and higher)</b> |                             |         |                             |         |                             |         |
| BMI (kg/m <sup>2</sup> )  |                             |         |                             |         |                             |         |
| 75 <sup>th</sup> quantile   | 1.7 (1.1, 2.2)              | <0.0001 | 3.6 (2.3, 4.9)              | <0.0001 | 1.3 (0.7, 1.8)              | <0.0001 |
| 90 <sup>th</sup> quantile   | 3.2 (2.4, 4.2)              | <0.0001 | 4.1 (1.9, 6.3)              | 0.0003  | 1.9 (1.1, 2.8)              | <0.0001 |
| 95 <sup>th</sup> quantile   | 3.3 (2.0, 4.7)              | <0.0001 | 5.3 (1.3, 9.2)              | 0.009   | 3.0 (1.7, 4.3)              | <0.0001 |
| Waist Circumference (cm)  |                             |         |                             |         |                             |         |
| 75 <sup>th</sup> quantile   | 5.0 (3.6, 6.4)              | <0.0001 | 6.4 (2.9, 9.9)              | 0.0004  | 3.6 (2.2, 5.0)              | <0.0001 |
| 90 <sup>th</sup> quantile   | 7.1 (5.1, 9.1)              | <0.0001 | 9.8 (4.1, 15.5)             | 0.0008  | 5.6 (3.1, 8.1)              | <0.0001 |
| 95 <sup>th</sup> quantile   | 9.1 (5.5, 12.7)             | <0.0001 | 9.6 (2.9, 16.3)             | 0.005   | 7.4 (3.7, 11.1)             | <0.0001 |
| Fasting Glucose (mg/dL)   |                             |         |                             |         |                             |         |
| 75 <sup>th</sup> quantile   | 1.0 (-0.4, 2.4)             | 0.18    | 0.0 (-3.0, 3.0)             | 1.0     | 1.0 (-1.3, 1.3)             | 1.0     |
| 90 <sup>th</sup> quantile   | 2.0 (-0.4, 4.4)             | 0.10    | 0.0 (-5.3, 5.3)             | 1.0     | 2.0 (0.5, 4.5)              | 0.12    |
| 95 <sup>th</sup> quantile   | 5.0 (0.8, 9.1)              | 0.02    | 14 (4.6, 23.4)              | 0.004   | 2.0 (-2.0, 6.0)             | 0.33    |

All results shown are weighted using inverse-probability-of-treatment-weights (IPTW). Covariates used to create inverse-probability-treatment-weights included: natal sex, age, race, CD4 count, eGFR (</> 90), smoking status, substance use, estrogen-containing preparations, testosterone-containing preparations, diet quality, physical activity level. Sex-stratified regressions used re-estimated IPTW excluding natal sex. Abbreviations: BMI, body mass index; LDL, low-density lipoprotein

**506 ASSESSMENT OF OBESITY AND METABOLIC PROFILE BY INTEGRASE INHIBITOR USE IN REPRIEVE**

**Emma Kileel<sup>1</sup>, Janet Lo<sup>1</sup>, Carlos Malvestutto<sup>2</sup>, Markella V. Zanni<sup>1</sup>, Kathleen Fitch<sup>1</sup>, Carl Fichtenbaum<sup>3</sup>, E. Turner Overton<sup>4</sup>, Nwora Lance Okeke<sup>5</sup>, Princy N. Kumar<sup>6</sup>, Esau Joao<sup>7</sup>, Pamela S. Douglas<sup>5</sup>, Judith A. Aberg<sup>8</sup>, Heather J. Ribaud<sup>9</sup>, Steven Grinspoon<sup>1</sup>**

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>The Ohio State University, Columbus, OH, USA, <sup>3</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>5</sup>Duke University School of Medicine, Durham, NC, USA, <sup>6</sup>Georgetown University, Washington, DC, USA, <sup>7</sup>HFSE-Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil, <sup>8</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>9</sup>Harvard TH Chan School of Public Health, Boston, MA, USA

**Background:** Among people with HIV (PWH), use of integrase inhibitor (InSTI)-based antiretroviral treatment (ART) has been associated with weight gain, but the health consequences of this weight gain remain unknown. Leveraging baseline data from a large, international cohort of ART-treated PWH eligible for primary cardiovascular disease (CVD) prevention, we investigated the association of InSTI vs. non-InSTI-based ART with body mass index (BMI), waist circumference (WC), fasting glucose and low-density lipoprotein (LDL).

**Methods:** The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) enrolled a global cohort of ART-treated PWH, aged 40-75 years with low-to-moderate traditional CVD risk. This cross-sectional analysis examined the effect of InSTI-use (>6 months) among participants in regions where at least 5% of the enrolled population were using InSTI-based regimens (High Income and Latin America/Caribbean Global Burden of Disease super regions). Primary analyses used linear and logistic regression; secondary analyses used quantile regression to examine differences in the distribution tails. Characteristics of those with and without entry InSTI-use were balanced by inverse probability of treatment weights (IPTW).

**Results:** Among 4498 enrolling in higher InSTI-use regions, 1847 were on an InSTI; 62% of the remainder were on a NNRTI, 36% a PI. Median age was 51 years (Q1-Q3: 46-55), 23% were natal female, 40% were Black/African American. Among participants on an InSTI, mean BMI was 28.2 kg/m<sup>2</sup> (±6.1kg/m<sup>2</sup>) and mean WC was 97.7cm (±14.8cm). IPTW regression showed higher mean BMI of +1.6kg/m<sup>2</sup> (95% CI: 1.2-1.9) and 65% higher odds of obesity (1.4-1.9) with InSTI-use compared to no InSTI-use. InSTI-use was also associated with higher WC (Table). This difference was greatest among natal females (+5.0cm (2.8-7.3) higher with InSTI-use compared to without). IPTW quantile regression suggested the greatest differences with InSTI-use were in the upper tails of BMI and WC distributions (Table). Parallel differences in fasting glucose and LDL were not apparent except at the 95th quantile of glucose among natal females (Table).

**Conclusion:** In an IPTW cross-sectional analysis, InSTI-use was associated with higher BMI, higher odds of obesity, and higher WC, especially among natal females, but largely not associated with elevated fasting glucose or LDL. Future longitudinal analyses of REPRIEVE participants on InSTI vs non-InSTI ART will help characterize long-term cardiometabolic effects of InSTI-use among PWH.

**507 ASSOCIATION BETWEEN NEWER ANTIRETROVIRALS AND INCREASE IN BODY MASS INDEX IN RESPOND**

**Loveleen Bansi-Matharu, for RESPOND**  
University College London, London, UK

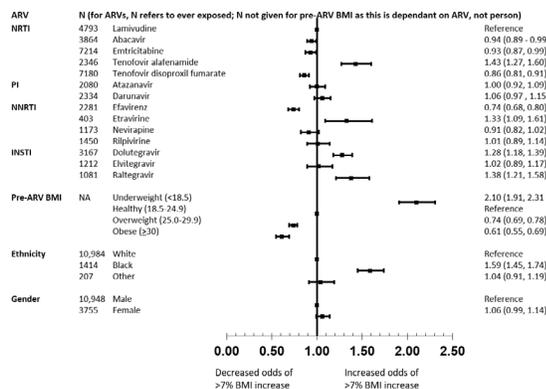
**Background:** Weight gain has been related to use of tenofovir alafenamide (TAF) and integrase inhibitor (InSTIs), particularly dolutegravir (DTG). However, the independent effects of individual contemporary antiretrovirals (ARVs) on weight gain are not fully understood. We investigated associations between pre-specified clinically significant increase (>7%) and extreme increase (>30%) in body mass index (BMI) and contemporary ARV use.

**Methods:** For all ARVs received on/after RESPOND study entry (median 2013), BMI changes from pre-ARV BMI levels (baseline) were considered at each BMI measured whilst on the ARV. The effect of each ARV was isolated by assuming each ARV was independent of other ARVs being received concomitantly. Logistic regression using generalised estimating equations to account for clustering was used to identify individual ARVs that were associated with first occurrence of >7% and >30% increase in BMI from pre-ARV BMI. Analyses were adjusted for time on ARV, pre-ARV BMI, demographics, geographical region, CD4 count, viral load, smoking status, diabetes, dyslipidaemia, hypertension, viral hepatitis, and clinical events at baseline. Analyses were also stratified according to receiving DTG with/without TAF and TAF with/without DTG.

**Results:** 14703 people were included (median 2.6 years follow-up), of whom 7863 (54%) had >7%, and 749 (5%) >30% BMI increase. At baseline 20% were ARV-naïve, 39% on InSTIs, 74% were male, 75% of white ethnicity and 45% MSM. Multivariate odds ratios (ORs) are shown in Figure 1. Use of DTG, raltegravir (RAL) and TAF, low pre-ARV BMI and black ethnicity were significantly associated with >7% BMI increase. ORs for people on both DTG and TAF (DTG 1.73 [1.47, 2.04], TAF 1.63 [1.38, 1.93] vs. lamivudine (3TC)) were higher than those taking DTG without TAF (1.20 [1.09, 1.31]) or TAF without DTG (1.30 [1.12, 1.50]). Both ARVs were independently associated with >30% BMI increase (DTG 2.02 [1.55, 2.62], TAF 2.09 [1.35, 3.22] vs. 3TC). When restricting to the 1476 naïve patients with pre-ART CD4 count>350, compared to 3TC, DTG was associated with >7% BMI increase (DTG 1.32 (1.11, 1.57)), but TAF was not (1.30 (0.96, 1.76)).

**Conclusion:** Low pre-ARV BMI was the strongest independent predictor of >7% BMI increase. Use of DTG, RAL and TAF were associated with significant BMI increase compared to 3TC independent of pre-ARV BMI and time on ARVs. Combined rather than individual use of TAF and DTG was associated with greater risk of BMI increase.

Figure 1: Multivariate odds ratios of 7% increase in BMI from pre-drug BMI



(Odds ratios for Amprenavir, Cobicistat, Stavudine, Didanosine, Fosamprenavir, Lopinavir, Maraviroc, Rilpivirine, Saquinavir and Zidovudine, unknown ethnicity not shown). Model also adjusted for time on ARV, age at baseline, risk group, region, CD4/VL at start of follow-up, smoking status, diabetes, dyslipidaemia, hypertension, viral hepatitis, and clinical events at start of follow-up.

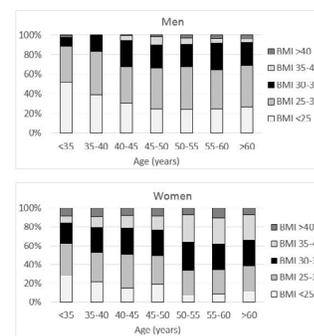


Figure 1: Overall prevalence of obesity in men and women by age

## 508 OBESITY IS HIGHLY PREVALENT IN PEOPLE OF AFRICAN ANCESTRY LIVING WITH HIV IN THE UK

Lisa Hamzah<sup>1</sup>, Rachel K. Hung<sup>2</sup>, Beatriz Santana-Suarez<sup>3</sup>, Zoe Ottaway<sup>3</sup>, Julie Fox<sup>2</sup>, Burns Fiona<sup>4</sup>, Sarah L. Pett<sup>5</sup>, Stephen Kegg<sup>6</sup>, Amanda Clarke<sup>7</sup>, Andrew Ustianowski<sup>8</sup>, Lucy Campbell<sup>9</sup>, Caroline Sabin<sup>9</sup>, Frank A. Post<sup>3</sup>, for the GEN-AFRICA Study Team

<sup>1</sup>St George's Hospital, London, UK, <sup>2</sup>King's College London, London, UK, <sup>3</sup>King's College Hospital, London, UK, <sup>4</sup>Royal Free Hospital, London, UK, <sup>5</sup>Mortimer Market Centre, London, UK, <sup>6</sup>Lewisham Hospital, London, UK, <sup>7</sup>Brighton and Sussex NHS Foundation Trust, Brighton, UK, <sup>8</sup>University of Manchester, Manchester, England, <sup>9</sup>University College London, London, UK

**Background:** Obesity is a global public health emergency, and people of African ancestry are disproportionately affected. Data on obesity, and associated health issues such as diabetes mellitus (DM) and hypertension (HPT), in African populations with HIV are relatively sparse. We determined the prevalence of, and factors associated with, obesity in the GEN-AFRICA cohort.

**Methods:** Participants were recruited from HIV clinics across England and were eligible if they self-identified as black, aged  $\geq 18$  years and willing to provide consent. Demographic and clinical data including a diagnosis of DM and HPT were obtained. Analyses were restricted to those with both parents born in the same African region (East/South/Central/West). Multivariable logistic regression was used to analyze factors ( $p < 0.1$  in univariable analysis) associated with obesity (BMI  $> 30$  kg/m<sup>2</sup>).

**Results:** A total of 2,341 individuals (mean age 48.0 [standard deviation 9.9] years, 62% female, median CD4 count 555 cell/mm<sup>3</sup>, 99% on ART, and 93.5% with HIV RNA  $< 200$  c/mL) were included. The proportion of participants currently exposed to NRTI, NNRTI, PI and INSTI was 93%, 38%, 32%, 31%, respectively. The overall prevalence of obesity was 44% (men 30% vs. women 52%) and increased with age (Figure 1). In univariable analysis, obesity was associated with demographic factors (age, gender, region of ancestry), HIV-associated factors (risk for HIV acquisition, CD4 count, HIV RNA, and exposure to efavirenz, raltegravir, tenofovir alafenamide (TAF) and abacavir (ABC)), and smoking status, diabetes, hypertension, cardiovascular disease (CVD) and chronic kidney disease (CKD). In multivariable analysis, age (aOR 1.07 [1.01, 1.13] per 5 years older, female gender (2.44 [2.00, 2.97]), East African ancestry (0.67 [0.53, 0.85]), HIV through vertical transmission (0.56 [0.33, 0.96]), CD4 cell count (1.03 [1.01, 1.04] per 50 cell increment), HPT (1.58 [1.28, 1.95]), current smoking (0.54 [0.37, 0.79]) and current abacavir use (0.79 [0.65, 0.96]) remained associated with obesity. No significant association with DM, CVD, CKD or exposure to efavirenz, TAF or integrase inhibitors was observed.

**Conclusion:** We report a high prevalence of obesity in African people with HIV, with older women particularly affected. Participants of East African ancestry and on ABC-containing regimens were less likely to be obese. Obesity management should be prioritized as part of medical care to people of African ancestry with HIV.

## 509 WEIGHT GAIN AMONG PARTICIPANTS STARTING DOLUTEGRAVIR-BASED HIV REGIMEN IN KENYA

Kassem Bourgi<sup>1</sup>, Susan Ofner<sup>1</sup>, Beverly Musick<sup>1</sup>, Bradley Griffith<sup>1</sup>, Lameck Diero<sup>2</sup>, Winnie Muyindike<sup>3</sup>, Rita Lyamuya<sup>4</sup>, Kara Wools-Kaloustian<sup>1</sup>, Constantin Yiannoutsos<sup>1</sup>, Samir Gupta<sup>1</sup>

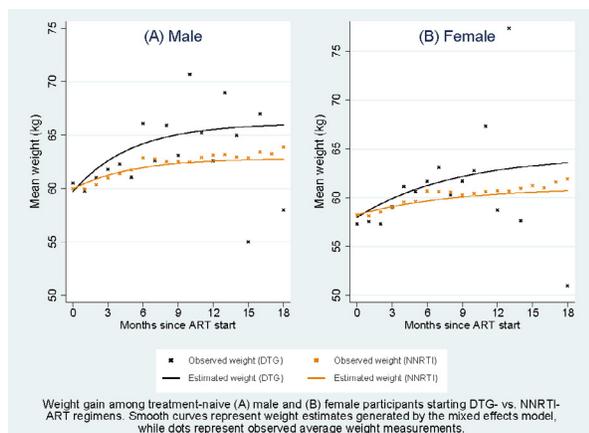
<sup>1</sup>Indiana University, Indianapolis, IN, USA, <sup>2</sup>Moi University, Eldoret, Kenya, <sup>3</sup>Mbarara University of Science and Technology, Mbarara, Uganda, <sup>4</sup>Morogoro Regional Hospital, Morogoro, Tanzania, United Republic of

**Background:** Weight gain following initiation of antiretroviral therapy (ART) is common among persons living with HIV. Integrase inhibitors, including dolutegravir (DTG), are now a critical component of ART and have been associated with increased risk for weight gain in several recent studies from North American, Europe and South Africa. In this study we aim to assess the impact of starting DTG-containing ART on weight gain in Kenya (a lower middle-income country) with high prevalence of HIV and recent large-scale roll-out of DTG.

**Methods:** Participants enrolled in the Academic Model Providing Access to Healthcare (AMPATH) program and starting their first ART regimen between 01/01/2015 and 09/30/2018 were enrolled in this study. Pregnant women were excluded. We compared weight gain over time between participants starting non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based regimens to DTG-based regimens. Participant data were censored if they switched their treatment regimen or experienced virologic failure after having documented viral suppression. Weights over the follow up period were modeled by a non-linear mixed effects model of decelerated exponential growth curve with random subject intercept. Starting weight, ending weight and rate of weight gain were adjusted for gender and drug group.

**Results:** 17,088 participants met inclusion criteria with 519 (3%) receiving DTG-based regimens compared to 16,569 (97%) receiving NNRTI-based regimens. Most of the participants were female (61%). At ART-initiation, participants had a median age of 37 years, median BMI of 20.8 kg/m<sup>2</sup>, and median CD4 T-cell count of 298 cells/mm<sup>3</sup>. At the end of study follow-up, participants starting DTG gained 3.5 kgs more than participants starting NNRTI-based regimens ( $p$ -value  $< 0.0001$ ). Male participants starting DTG had a significantly higher baseline weight compared to female participants (59.7kg vs. 58.0kg,  $p$ -value  $< 0.001$ ). Both groups experienced similar weight gain with DTG (6.4 kg for males, 6.3 kg for females,  $p$ -value = 0.250).

**Conclusion:** In a large HIV cohort from Kenya, DTG-based regimens were associated with greater weight gain compared to traditional NNRTI-based regimens. Interestingly, contrary to what has been reported in several US and South African studies, weight gain with DTG was not significantly different between men and women during the study's duration.



## 510 WEIGHT GAIN POST-ART IN HIV+ LATINOS/AS DIFFERS IN THE US, CANADA, AND LATIN AMERICA

Lara Coelho<sup>1</sup>, Cathy A. Jenkins<sup>2</sup>, Bryan Shepherd<sup>2</sup>, Jean W. Pape<sup>3</sup>, Fernando Mejia<sup>4</sup>, Denis Padgett<sup>5</sup>, Brenda Crabtree Ramirez<sup>6</sup>, Beatriz Grinsztejn<sup>1</sup>, Keri N. Althoff<sup>7</sup>, John Koethe<sup>2</sup>, Vincent Marconi<sup>8</sup>, Phyllis Tien<sup>9</sup>, Amanda Willig<sup>10</sup>, Catherine McGowan<sup>2</sup>, Peter F. Rebeiro<sup>2</sup>

<sup>1</sup>Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, <sup>2</sup>Vanderbilt University, Nashville, TN, USA, <sup>3</sup>GHEKIO, Port-au-Prince, Haiti, <sup>4</sup>Instituto de Medicina Tropical Alexander von Humboldt, Lima, Peru, <sup>5</sup>Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras, <sup>6</sup>Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, <sup>7</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>8</sup>Emory University, Atlanta, GA, USA, <sup>9</sup>University of California San Francisco, San Francisco, CA, USA, <sup>10</sup>The University of Alabama at Birmingham, Birmingham, AL, USA

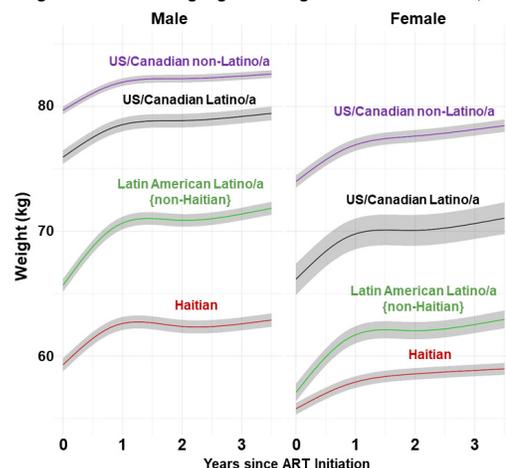
**Background:** The obesity epidemic has been observed in the adult general population of Latin America (24% obese), however little is known about obesity among persons with HIV (PWH) in Latin America (LAm). Moreover, Latino/a PWH in the US and Canada (US/C) may have different weight trajectories than those in LAm due to environmental context. We therefore assessed weight gain after antiretroviral therapy (ART) initiation and associated factors in PWH in the Americas, with contrasts between LAm and US/C Latino/a PWH and non-Latino/a PWH.

**Methods:** We included ART-naïve, PWH  $\geq 18$  years old enrolled at CCASnet or NA-ACCORD sites 2000–2016, starting ART, and with weight measures before/after ART initiation. Baseline weight was that closest to ART initiation ( $-180$  to  $+30$  days); weights at 1 and 3 years post-ART were those closest to these time points ( $\pm 180$  days). Generalized least squares models were used to assess trends in weight by site/ethnicity. Covariates included were age, sex, year of ART initiation, ART regimen, and weight, CD4, and viral load at ART initiation.

**Results:** Among 60,831 PWH, 69% were US/C non-Latino/a, 8% US/C Latino/a, 9% Latino/a in LAm, and 14% Haitians. At ART initiation, 10.0% were obese ( $\text{BMI} \geq 30$ ): 11.7% of US/C non-Latino/a, 10.9% of US/C Latino/a, 3.8% of Latino/a in LAm, and 5.1% of Haitians. At 3-years post-ART, average weight gain among men was: 2.8 kg in US/C non-Latinos, 3.2 kg in US/C Latinos, 6.2 kg in Latinos in LAm, and 4.1 kg in Haitians. Average weight gain among women was: 4.2 kg in US/C non-Latinas, 3.5 kg in US/C Latinas, 5.2 kg in Latinas in LAm, and 0.3 kg in Haitians (Figure; global  $p < 0.01$  for men and women). In LAm, Peruvian men had the greatest weight gain at 3 years, followed by Brazilians, Mexicans, and Hondurans; Brazilian women gained the most at 3 years, followed by Peruvians and Hondurans. Overall weight gain was steepest at 1 year post-ART. Use of PI-based regimens, higher CD4, and lower viral load at baseline were associated with lower post-ART weight gain.

**Conclusion:** In the Americas, PWH substantially gain weight after ART initiation. Observed post-ART weight gain trajectories were steeper for Latinos/as in LAm and Haitian men. Initial prevalence of obesity coupled with observed weight gain suggest there may be a healthy "catch-up" phenomenon among Latino/a PWH in LAm relative to the US/C, though changes in BMI must also be examined. Nutrition and healthy migrant effects may help explain these differences.

Figure. Post-ART weight gain among PWH in the Americas, 2000–2016



## 511 CHARACTERISTICS OF HIV+ AND HIV- PATIENTS UNDERGOING BARIATRIC SURGERY: OBEVIH STUDY

Valérie Pourcher<sup>1</sup>, Yasmine Dudoit<sup>1</sup>, Jacqueline Capeau<sup>1</sup>, Franck Boccard<sup>1</sup>, Cathia Soulie<sup>1</sup>, Aude Ndoadoumgué<sup>2</sup>, Frédéric Charlotte<sup>1</sup>, Véronique Béréziat<sup>3</sup>, Anne Genevieve Marcelin<sup>1</sup>, Gilles Peytavin<sup>1</sup>, Marie-Christine Boutron-Ruault<sup>4</sup>, Dominique Costagliola<sup>2</sup>, Christine Katlama<sup>1</sup>, Lambert Assoumou<sup>2</sup>, Guillaume Pourcher<sup>5</sup>

<sup>1</sup>Assistance Publique—Hôpital de Paris, Paris, France, <sup>2</sup>INSERM 1136, Paris, France, <sup>3</sup>INSERM, Paris, France, <sup>4</sup>INSERM U 1018, Villejuif, France, <sup>5</sup>Institut Mutualiste Montsouris, Paris, France

**Background:** Bariatric surgery (BS) is a major strategy to manage patients with morbid obesity which needs to be comparatively evaluated in HIV+ and HIV- patients.

**Methods:** ObeVIH is a prospective ongoing study of HIV+ patients with  $\text{BMI} > 35 \text{ kg/m}^2$ , with comorbidities, or  $> 40 \text{ kg/m}^2$ , and plasma HIV-RNA  $< 20$  copies/ml undergoing single port sleeve gastrectomy. We compared HIV+ and HIV- groups matched 1:1 on age, sex, and BMI and evaluated the impact of HIV/ART on subcutaneous (SCAT), visceral adipose tissue (VAT) and liver histology. During BS, VAT/SCAT was recovered and scored for inflammation (macrophage crown-like structure)/peri-lobular fibrosis/peri-adipocyte fibrosis, and liver biopsies were scored for steatosis/inflammation/fibrosis. We report here patients' baseline characteristics including comorbidities and cardiovascular (CV) parameters: echocardiography findings (left ventricular mass index (LVMI) and ejection fraction (LVEF)), and coronary calcium score (CCS).

**Results:** ObeVIH enrolled a total of 40 patients: 19 HIV- and 21 HIV+ with median (IQR) ART duration: 15y (7.5–17.5), viral suppression duration: 3.5y (2–6), and CD4 count:  $864/\text{mm}^3$  (560–1066). ART was InSTI-Based in 15 and PI/NNRTI based in 6. The anthropometric, CV, adipose tissue and liver characteristics are presented in Table 1. No difference in the prevalence of sleep apnea, hypertension, diabetes, liver/bone/kidney diseases, dyslipidemia was observed. Moreover, there was no difference between groups for LVMI ( $p=0.506$ ), LVEF ( $p=0.371$ ), and CCS ( $p=1.00$ ). In adipose tissue, the level of inflammation was lower in SCAT of InSTI-treated subjects than in HIV- ( $p=0.02$ ) and non-InSTI-treated HIV+ ( $p=0.07$ ). NASH was diagnosed by SAF score in 1/14 InSTI-treated, 2/6 non-InSTI treated HIV+ and 1/16 HIV-. The level of liver steatosis was lower in InSTI-treated than non-InSTI treated HIV+ ( $p=0.05$ ). There was no overall difference between HIV+ and HIV- patients.

**Conclusion:** We report here that HIV+ and HIV- subjects undergoing BS presented a similar profile regarding baseline CV parameters and prevalence of comorbidities. However, there were differences between InSTI- and non-InSTI treated HIV+ in SCAT and liver histology. None InSTI-treated patients had inflammation in SCAT while it was present in some non-InSTI treated HIV+ and HIV- patients, which could suggest an anti-inflammatory effect of InSTI. Moreover, liver histology showed a milder profile with less steatosis in InSTI-treated than non-InSTI treated HIV+.

|   | HIV- (n=19)                 | HIV+ (n=21)          | P value |
|---|-----------------------------|----------------------|---------|
| Age, years                                | 43.0 (37.0, 51.0)           | 48.0 (42.0, 51.0)    | 0.506   |
| Sex                                       | women 15 (78.9%)            | 16 (76.2%)           | 1.00    |
|   | men 4 (21.1%)               | 5 (23.8%)            |         |
| Birth Country                             | Sub sahara Africa 6 (31.6%) | 15 (71.4%)           | 0.012   |
|   | Other 13 (68.4%)            | 6 (28.6%)            |         |
| Maximal weight MW (kg)                    | 116.0 (105.0, 136.0)        | 118.0 (107.0, 125.0) | 0.881   |
| Age at MW (kg)                            | 38.0 (30.0, 45.0)           | 47.0 (40.0, 50.0)    | 0.058   |
| Baseline body weight (kg)                 | 110.0 (93.3, 132.0)         | 113.0 (104.0, 120.7) | 0.533   |
| Baseline BMI (kg/m <sup>2</sup> )         | 39.2 (36.3, 42.6)           | 41.4 (37.3, 44.4)    | 0.228   |
| Limb fat mass (kg)                        | 26.0 (20.0, 30.0)           | 21.0 (19.0, 32.0)    | 0.464   |
| Lean body mass(kg)                        | 27.0 (22.0, 30.0)           | 27.0 (22.0, 31.0)    | 0.903   |
| Trunk fat mass (kg)                       | 24.0 (23.0, 27.0)           | 24.0 (21.0, 26.0)    | 0.471   |
| Trunk lean mass(kg)                       | 28.0 (25.0, 33.0)           | 30.0 (26.0, 31.0)    | 0.423   |
| Total fat mass (kg)                       | 49.0 (43.0, 55.0)           | 45.0 (40.0, 58.0)    | 0.357   |
| Total lean mass (kg)                      | 56.0 (47.0, 62.0)           | 53.0 (46.0, 67.0)    | 0.654   |
| Left ventricular mass index (LVMI)        | 70.8 (57.7, 80.8)           | 60.6 (48.4, 78.0)    | 0.506   |
| Left ventricular ejection fraction (LVEF) | 60 (60, 60)                 | 60 (60, 60)          | 0.371   |
| Coronary calcium score (CCS)              | 0.0 (0.0, 0.0)              | 0.0 (0.0, 1.8)       | 1.00    |
| VAT inflammation                          | 0.37 (0.14)                 |                      |         |
| - Total HIV+                              | 0.43 (0.11)                 |                      | 0.655   |
| - INStI-treated                           | 0.47 (0.13)                 |                      | 0.484   |
| - non-INStI treated                       | 0.33 (0.21)                 |                      | 0.999   |
| VAT peri-lobular fibrosis                 | 1.05 (0.18)                 |                      |         |
| - Total HIV+                              | 0.90 (0.15)                 |                      | 0.655   |
| - INStI-treated                           | 0.87 (0.17)                 |                      | 0.477   |
| - non-INStI treated                       | 1.00 (0.36)                 |                      | 0.989   |
| VAT peri-adipocyte fibrosis               | 0.53 (0.12)                 |                      |         |
| - Total HIV+                              | 0.70 (0.16)                 |                      | 0.597   |
| - INStI-treated                           | 0.79 (0.19)                 |                      | 0.301   |
| - non-INStI treated                       | 0.50 (0.34)                 |                      | 0.733   |
| SCAT inflammation                         | 0.32 (0.11)                 |                      |         |
| - Total HIV+                              | 0.10 (0.07)                 |                      | 0.120   |
| - INStI-treated                           | 0.00 (0.5)                  |                      | 0.824   |
| - non-INStI treated                       | 0.33 (0.21) §               |                      | 0.999   |
| SCAT peri-lobular fibrosis                | 1.42 (0.19)                 |                      |         |
| - Total HIV+                              | 1.67 (0.14)                 |                      | 0.366   |
| - INStI-treated                           | 1.53 (0.19)                 |                      | 0.794   |
| - non-INStI treated                       | 2.00 (0.0)                  |                      | 0.156   |
| SCAT peri-adipocyte fibrosis              | 0.74§ (0.18)                |                      |         |
| - Total HIV+                              | 1.10 (0.18)                 |                      | 0.161   |
| - INStI-treated                           | 1.07 (0.22)                 |                      | 0.264   |
| - non-INStI treated                       | 1.17 (0.31)                 |                      | 0.281   |
| Liver steatosis                           | 1.00 (0.26)                 |                      |         |
| -Total HIV+                               | 0.80 (0.20)                 |                      | 0.614   |
| -INStI-treated                            | 0.50 (0.17) §               |                      | 0.195   |
| -non-INStI-treated                        | 1.5 (0.43) §                |                      | 0.322   |
| Liver inflammation                        | 0.69 (0.25)                 |                      |         |
| -Total HIV+                               | 0.95 (9.22)                 |                      | 0.217   |
| -INStI-treated                            | 0.79 (9.21)                 |                      | 0.471   |
| -non-INStI-treated                        | 1.33 (0.56)                 |                      | 0.117   |
| Liver fibrosis                            | 0.27 (0.15)                 |                      |         |
| -Total HIV+                               | 0.10 (0.07)                 |                      | 0.525   |
| -INStI-treated                            | 0.07 (0.07)                 |                      | 0.531   |
| -non-INStI-treated                        | 0.17 (0.17)                 |                      | 0.886   |
| Liver fibrosis                            | 0.27 (0.15)                 |                      |         |
| -Total HIV+                               | 0.10 (0.07)                 |                      | 0.525   |
| -INStI-treated                            | 0.07 (0.07)                 |                      | 0.531   |
| -non-INStI-treated                        | 0.17 (0.17)                 |                      | 0.886   |

All results are presented as median (IQR) for patients' characteristics or mean (SEM) for adipose tissue and liver parameters. Statistical analysis was performed using Mann-Whitney test: § p<0.05 between INI and non-INI-treated patients; § p<0.07 between INI and non-INI-treated patients. Table 1: Patients characteristics at inclusion and scores of inflammation, peri-lobular and peri-adipocyte fibrosis in VAT and SCAT biopsies and of steatosis, inflammation and fibrosis in liver biopsies recovered during BS from HIV-infected and non-infected patients enrolled in the ObeV17 study.

## 512 METABOLOMIC SIGNATURES DIFFERENTIATE WOMEN WHO GAIN WEIGHT WITH INTEGRASE INHIBITORS

**Cecile D. Lahiri<sup>1</sup>**, Anandi N. Sheth<sup>1</sup>, Cyra C. Mehta<sup>1</sup>, Renata M. Shaw<sup>1</sup>, Vilinh Tran<sup>1</sup>, Young-Mi Go<sup>1</sup>, Dean P. Jones<sup>1</sup>, Thomas R. Ziegler<sup>1</sup>, Igbo Ofotokun<sup>1</sup>, Jessica A. Alvarez<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA

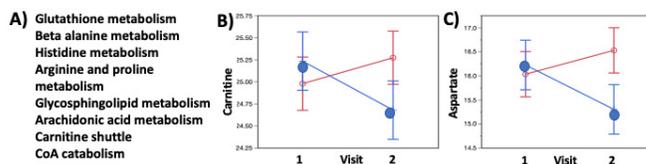
**Background:** Integrase strand-transfer inhibitors (InSTIs) are associated with body weight gain in women living with HIV (WLH). Emerging evidence suggests that InSTIs dysregulate insulin signaling, leading to insulin resistance and excess fat storage. We compared early changes in metabolomic profiles after a switch to InSTIs among women who later gained or did not gain weight.

**Methods:** We studied virally-suppressed (<200 copies/mL) WLH from the Atlanta Women's Interagency HIV Study who switched to an InSTI. Data from 3 visits were used: Visit 1=pre-switch, Visit 2=within 6 months of switch, Visit 3=4-13 months after Visit 2. Stored plasma samples from Visits 1 and 2 were analyzed in triplicate with high-resolution mass spectrometry using positive electrospray ionization (ESI) with hydrophilic interaction liquid chromatography and negative ESI with C18 chromatography. Body weight change was the difference in weight from Visit 3 and Visit 1. Change in metabolomic signature (Visit 1 to Visit 2) were compared in women who experienced ≥ 5% weight gain versus those who maintained/lost weight using two-way repeated measures ANOVA.

**Results:** Thirty-three WLH with ≥ 5% body weight gain (n=18) or weight maintenance/loss (n=15) after switching to InSTIs were included in the analyses. Mean age was 50 yrs (± 8), 94% Black, baseline BMI 34.1 kg/m<sup>2</sup> (±9.5), and this was similar between groups. A total of 519 metabolites had a significant group x time interaction effect (p<0.05). Pathway enrichment analysis identified metabolic pathways that differentially changed after InSTI initiation in women who later gained vs maintained/lost weight, including

the bioenergetic pathways carnitine shuttle and CoA catabolism, and amino acids pathways (Figure 1). The annotated metabolites, plasma carnitine and aspartate, significantly increased following InSTI initiation in women who later experienced ≥ 5% body weight gain but not in those with weight maintenance/loss.

**Conclusion:** Significant changes in amino acid pathways are reflective of insulin resistance and causative of body weight gain following a switch to InSTIs. Changes in bioenergetic pathways suggests altered mitochondrial utilization of fuels, or metabolic inflexibility, induced by InSTI use among those who later gain weight. Because these metabolomic changes occurred soon after InSTI initiation and prior to weight change, these data provide mechanistic insight into InSTI-specific body weight changes over 1-2 years and should be validated in a larger population.



**Figure 1.** A) Pathway enrichment analysis of metabolites significantly and differentially changing following switch to InSTIs but prior to weight gain. B-C) Selected metabolites from significant metabolic pathways that increased in women with weight gain but not weight maintenance/loss. Visit 1 = pre- InSTI switch; Visit 2 = within 6 months of switch. Open red circles = ≥ 5% weight gain; Filled blue circles = weight maintenance/ loss 1-2 years post InSTI switch.

## 513 URINE MITOCHONDRIAL DNA, WEIGHT LOSS, AND BODY COMPOSITION IN OLDER ADULTS WITH HIV

**Carrie Johnston<sup>1</sup>**, Eugenia Siegler<sup>1</sup>, Michelle Rice<sup>1</sup>, Heather Derry<sup>1</sup>, Katie Hootman<sup>1</sup>, Yuan-Shan Zhu<sup>1</sup>, Chelsie Burchett<sup>1</sup>, Mary Choi<sup>1</sup>, Marshall J. Glesby<sup>1</sup>

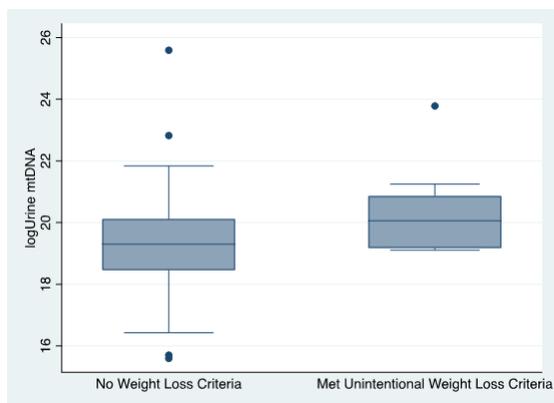
<sup>1</sup>Weill Cornell Medicine, New York, NY, USA

**Background:** Mitochondrial DNA released from cells undergoing stress and necrosis-mediated cell death has the potential to act both as mediator and marker of inflammatory dysregulation, and to serve as a biomarker in the blood and urine. We hypothesized that urine cell-free mitochondrial DNA (cfmtDNA) would be associated with geriatric syndromes in older adults with HIV (OAH).

**Methods:** This is a cross sectional analysis of OAH (age 55 and over) who had frailty testing (Fried Frailty phenotype), bioelectric impedance analysis (BIA), and measurement of urine cfmtDNA by quantitative PCR. Skeletal muscle and fat mass indices were calculated using BIA results.

**Results:** Of 164 participants, there were 109 (66%) males, the mean age was 61 years (SD 6), 82 (52%) identified as Black, and 93% had HIV-1 viral load <200 copies/mL. Urine cfmtDNA was measured in 150 participants who had urine available for analysis. The geometric mean cfmtDNA level in urine was 2.4x10<sup>8</sup> copies/gram of urine creatinine [95%CI: 2.0x10<sup>8</sup>-3.1x10<sup>8</sup>]. Two thirds (67%) met criteria for a pre-frail or frail state. Mean urine cfmtDNA level was higher in participants who met frailty criteria for unintentional weight loss (p=0.01) by t-test [Figure 1]. Other frailty components including slow walk, weak grip, exhaustion and low physical activity did not have statistically significant differences in mean urine mtDNA level (p-values > 0.31). In a multivariable linear regression model both microalbuminuria (p<0.001) and age (p = 0.01) were associated with higher urine cfmtDNA values, whereas sex, diabetes, and use of angiotensin I converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) medications did not have statistically significant relationships with urine mtDNA levels (p=0.16, p=0.42, p=0.44, respectively). In a sample subset with body composition data (n=138), median body mass index was in the overweight range (median=27kg/m<sup>2</sup>, IQR 24-31). In separate multiple linear regression models adjusted for age, sex and microalbuminuria, higher urine cfmtDNA was inversely associated with skeletal muscle index (SMI) (β = -0.19, p<0.01) as well as fat mass index (FMI) (β = -0.08, p=0.02).

**Conclusion:** Urine cfmtDNA may have a role as a novel biomarker of geriatric syndromes in OAH that may feature unintentional weight loss and lower skeletal muscle and fat mass indices.



## 514 IN VITRO MODEL TO ASSESS ANTIRETROVIRAL THERAPY ON ADIPOCYTE BIOLOGY

R. Taylor Pickering<sup>1</sup>, Archana Asundi<sup>1</sup>, Nina Lin<sup>1</sup>

<sup>1</sup>Boston Medical Center, Boston, MA, USA

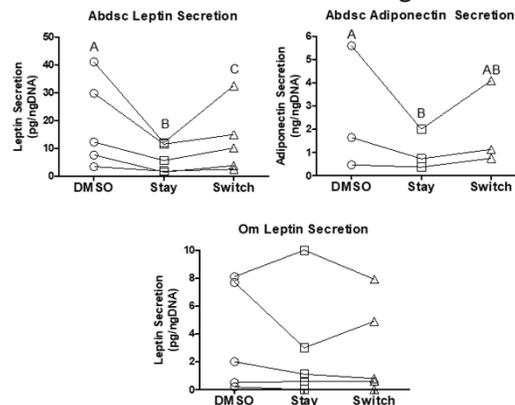
**Background:** Antiretroviral therapies (ART) have diverse effects on adipose tissue biology, clinically observed through changes in weight and fat distribution with ART initiation or switch. These effects likely occur in a fat depot-specific manner, however the mechanisms remain poorly understood. Our objective was to develop an in-vitro model which allows in-depth examination of the cellular effects of specific ART regimens on adipocyte biology.

**Methods:** We utilized five paired human preadipocyte cultures from omental (Om) and abdominal subcutaneous (Abdsc) depots from HIV uninfected individuals to examine effects of an integrase-inhibitor (InSTI); dolutegravir (DTG), compared to a protease inhibitor; Darunavir (DRV), on adipocytes. Cells were differentiated for 7 days using an adipogenic medium. After 7 days, adipocytes were switched to a maintenance media and treated with DMSO (Control) or DTG, 3.1µg/mL for 7 days. Adipocytes were then maintained on DTG (STAY) or switched to DRV, 11.8µM, (SWITCH) until day 21. Triglyceride content was assessed by enzymatic assay and normalized to DNA content. Adipogenic and fibrotic gene expression was assessed using RT-qPCR, and adipokine secretion was determined with ELISA

**Results:** In both Om and Abdsc cells, exposure to DTG and DRV did not affect viability. Triglyceride accumulation did not differ between ART exposures. Adipocytes in the STAY condition had significantly increased expression of PPAR $\gamma$ , a late adipogenic marker, in both Om and Abdsc adipocytes (1.6 fold & 1.3 fold,  $p < 0.05$ ) and did not diminish with SWITCH. Expression of collagen-6 mRNA, a fibrotic marker, was increased in the STAY condition in Abdsc (1.4 fold,  $p < 0.05$ ) but not Om. Both leptin and adiponectin (ADCN) secretion were significantly decreased in the STAY condition (6.6pg leptin/ngDNA vs. 18.9pg; 1.0pg ADCN/ngDNA vs. 2.6pg,  $p < 0.05$ ), and this was partially ameliorated in the SWITCH condition (12.8ng leptin; 2.0pg ADCN,  $p < 0.05$ ) in Abdsc but not in Om adipocytes (Image)

**Conclusion:** We developed an in-vitro model using differentiated primary human adipocytes which can examine differential depot-dependent effects of specific ART on adipocyte biology. The observed decrease in leptin, a major satiety hormone, in the STAY group may help explain the increased weight gain observed in individuals taking InSTIs. This model can help define mechanisms by which ART causes adverse metabolic effects and used in pre-clinical applications to test potential, unintended adipocyte-specific effects of future ART.

## Adipokine secretion following treatment with antiretroviral drugs



## 515 INTEGRASE INHIBITORS TARGET MITOCHONDRIA IN BROWN ADIPOCYTES DISRUPTING THERMOGENESIS

Ikraek Jung<sup>1</sup>, Sunghye Jin<sup>1</sup>, Becky Tu-Sekine<sup>1</sup>, Fredrick Anokye-Danso<sup>1</sup>, Todd Brown<sup>1</sup>, Sangwon F. Kim<sup>1</sup>

<sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Antiretroviral therapy (ART) containing integrase strand transfer inhibitors (InSTI) has been associated with weight gain in both ART-initiation and switch studies, especially in women, but the underlying mechanisms are unclear. Estrogen promotes brown adipocyte differentiation while suppressing white adipocyte differentiation. Hence, we hypothesized that InSTIs may interrupt adipose function via inhibition of estrogen action.

**Methods:** Primary preadipocytes were isolated from 4 weeks female mouse (C57BL/6). Cells were treated with InSTI (dolutegravir (DTG) or bicitegravir (BIC)) or doravirine (DOR) for 8 days during differentiation into mature white or brown adipocytes. Mature adipocytes were analyzed for lipid accumulation by Oil Red O Staining, adipogenic markers by qRT-PCR and immunoblotting. Estrogen receptor mediated transcriptional activity was measured by Luciferase reporter containing estrogen response element. Finally, we examined the effects of DTG (10mg/kg for 5 days) on food intake, energy expenditure, oxygen consumption in female mice using Comprehensive Laboratory Animal Monitoring System.

**Results:** We found that DTG and BIC mildly induced white adipocyte differentiation measured by white adipogenic markers (SREBP, CEBP $\alpha$ , and PPAR $\gamma$ ) and lipid accumulation. In contrast, brown adipogenic markers (CEBP $\beta$ , PGC1 $\alpha$  and FABP4) were significantly reduced by DTG or BIC exposure (50-80%). Uncoupling protein1 (UCP1), which is an essential for a thermogenic process in brown/beige adipocytes, was downregulated by more than 90% compared to no treatment group. In addition, a decrease in UCP1 in brown adipocytes was accompanied by a decrease in cytochrome oxidase complex IV (COX IV) in mitochondria as well as GAPDH, a key glycolytic enzyme. Moreover, estrogen receptor-reporter assay revealed that estrogen-mediated pathway was blocked by DTG by 70%. DOR had no effect on fat differentiation, UCP1 expression, or mitochondrial enzyme activity. In vivo, DTG administration to female mice inhibited oxygen consumption and energy expenditure by 15% without affecting food consumption.

**Conclusion:** In in vitro models, InSTI exposure had opposite effects on the differentiation of white and brown fat. In brown adipocytes, the inhibition of brown thermogenic function by DTG was associated with interruption of mitochondrial proteins (e.g. COX IV and UCP1), which may be mediated through estrogen receptor. These findings suggest a novel mechanism by which InSTIs may lead to weight gain, especially in women.

## 516 INCIDENT DIABETES ASSOCIATED WITH INTEGRASE STRAND TRANSFER INHIBITOR INITIATION

Jane O'Halloran<sup>1</sup>, John Sahrman<sup>1</sup>, Margaret Olsen<sup>1</sup>, William Powderly<sup>1</sup>

<sup>1</sup>Washington University in St Louis, St Louis, MO, USA

**Background:** Integrase strand transfer inhibitors (InSTIs), in particular dolutegravir, have been associated with weight gain in people with HIV (PWH). However, limited data exists on other metabolic outcomes in PWH on this class of ART. We examined the risk of new-onset diabetes mellitus and hyperglycemia in PWH on InSTI-based regimens.

**Methods:** Data from the IBM® MarketScan® databases for commercially and Medicaid insured adults were used to identify PWH on ART. The date of initiation or switch to InSTI was used as the index date for InSTI users while the date of initiation or 180 days after the first claims (for prevalent users) was used for non-InSTI users. The primary outcome was a composite of new-onset diabetes mellitus or hyperglycemia in the six months post-ART initiation. We identified outcomes and covariates associated with risk of diabetes mellitus and hyperglycemia using ICD-9-CM/ICD-10-CM diagnosis and procedure codes and CPT-4 codes. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for association between new-onset diabetes and hyperglycemia and overall or individual InSTI use.

**Results:** 111, 652 PWH initiated ART between Jan 1, 2007 and June 30, 2018. 34,398 (31%) were treated with InSTI-based regimens (raltegravir 37.7%, elvitegravir 35.5%, dolutegravir 26.8%). Mean age was 42.3 (standard deviation 10.9) years, 78% were male, and 16% were Medicaid insured. The primary outcome occurred in 2,836 PWH (93% new-onset diabetes mellitus, 7% hyperglycemia). PWH on InSTIs were 22% more likely to develop new-onset diabetes mellitus or hyperglycemia (HR 1.22 [95% CI 1.13, 1.32]). When InSTIs were included in the model individually, PWH on dolutegravir were 47% more likely to develop new-onset diabetes mellitus or hyperglycemia (HR 1.47 [95% CI 1.31, 1.66]), while those on elvitegravir were 20% more likely (HR 1.20 [95% CI 1.01, 1.34]). No association was observed in those on raltegravir-based therapy (HR 1.04 [95% CI 0.92, 1.17]).

**Conclusion:** Overall, InSTI use was associated with increased risk of new-onset diabetes mellitus or hyperglycemia in the six months post index. The risk was more than twice as high in those on dolutegravir compared with those on elvitegravir while raltegravir was not associated with this finding. Further research is necessary to understand the mechanism driving these findings.

## 517 PREDICTED 10-YEAR RISKS OF CARDIOVASCULAR DISEASE AND DIABETES IN THE ADVANCE TRIAL

Laura Hindley<sup>1</sup>, Kaitlyn Mccan<sup>1</sup>, Simiso Sokhela<sup>2</sup>, Nomathemba Chandiwana<sup>2</sup>, Francois Venter<sup>2</sup>, Celia M. Serenata<sup>3</sup>, Andrew Hill<sup>3</sup>

<sup>1</sup>Imperial College London, London, UK, <sup>2</sup>Ezintsha, Johannesburg, South Africa, <sup>3</sup>University of Liverpool, Liverpool, UK

**Background:** In the ADVANCE trial, more participants developed obesity on TAF/FTC+DTG vs TDF/FTC+DTG and TDF/FTC/EFV. Overweight and obesity are associated with elevated risk of cardiovascular disease (CVD) and type 2 diabetes (T2D). This study aimed to quantify these risks using standard risk algorithms. New analysis of the FDA FAERS database showed more reports of myocardial infarction (MI)/T2D for people on integrase inhibitors. Plasma EFV concentrations have been associated with raised glucose concentrations in HIV-infected South Africans.

**Methods:** In ADVANCE, 1053 treatment-naïve participants (99% black, 56% female, 62% South African) were randomised to 192 weeks of TAF/FTC+DTG, TDF/FTC+DTG or TDF/FTC/EFV. Body weight change was evaluated to week 144. Low-density lipoprotein, high-density lipoprotein, total cholesterol, fasting glucose and systolic blood pressure were measured at baseline, week 96 and week 144. These variables were used to calculate the 10-year risk of CVD (MI/stroke) and T2D based on weight change to week 144 using the QRISK, Framingham (BMI-based) and QDiabetes risk algorithms. QRISK and QDiabetes were adjusted for black African race. Participants ≥30 years with laboratory data for parameters in the risk equations were included. Differences between groups were tested using non-parametric methods.

**Results:** 397, 386 and 374 participants were included in Framingham, QRISK and QDiabetes respectively. Vital signs and laboratory parameters were similar at baseline between arms. Mean weight gain to week 144 was +9.5kg (TAF/FTC+DTG), +6.1kg (TDF/FTC+DTG), +3.6kg (TDF/FTC/EFV). At week 144, participants on TAF/FTC+DTG had greater predicted 10-year risk of developing CVD compared to TDF/FTC/EFV (p=0.016), and of T2D compared to TDF/FTC+DTG (p=0.024) (Table 1). CVD risk was greater for men, T2D risk was greater for women. From QRISK, CVD risk was 0.02% greater for women on TAF/FTC+DTG vs TDF/FTC/EFV. For men, this risk increase was 0.2%, equivalent to 2 additional MI/stroke cases/ 1000 men. Predicted T2D risk was greater for women on TAF/FTC+DTG vs TDF/FTC+DTG by 0.9%, equivalent to 9 additional T2D cases/ 1000 women. For men, this increase was 0.75% or 7.5 additional T2D cases/ 1000 men.

**Conclusion:** Treatment-emergent weight gain, particularly on TAF/FTC+DTG, increased participants' predicted 10-year risk of developing CVD and T2D. These

results support WHO recommendations for TDF/FTC+DTG as 1st-line therapy, with TAF/FTC+DTG only used for patients with osteoporosis or renal impairment.

Table 1.0: Summary of risk score changes from baseline to week 144. All participants ≥30 years old at baseline.

| Risk Equation    |                    | Arm 1 (TAF/FTC+DTG) |                    | Arm 2 (TDF/FTC+DTG) |                    | Arm 3 (TDF/FTC/EFV) |                    | P-value Arm 1 vs Arm 3 | P-value Arm 1 vs Arm 2 | P-value Arm 2 vs Arm 3 |
|------------------|--------------------|---------------------|--------------------|---------------------|--------------------|---------------------|--------------------|------------------------|------------------------|------------------------|
|                  |                    | n                   | Median (Q1, Q3)    | n                   | Median (Q1, Q3)    | n                   | Median (Q1, Q3)    |                        |                        |                        |
| Framingham (CVD) | Baseline           | 216                 | 2.63 (1.63,4.57)   | 218                 | 2.70 (1.70,5.42)   | 215                 | 2.64 (1.60,4.35)   |                        |                        |                        |
|                  | Change to week 144 | 139                 | +1.37 (0.56, 2.77) | 133                 | +1.02 (0.38, 2.05) | 125                 | +0.96 (0.46, 2.33) | 0.034                  | 0.038                  | 0.982                  |
| QRISK (CVD)      | Baseline           | 216                 | 0.60 (0.30,1.00)   | 218                 | 0.50 (0.30,1.10)   | 215                 | 0.50 (0.30,1.00)   |                        |                        |                        |
|                  | Change to week 144 | 131                 | +0.36 (0.14, 0.80) | 139                 | +0.25 (0.10, 0.65) | 116                 | +0.20 (0.10, 0.60) | 0.016                  | 0.113                  | 0.377                  |
| QDiabetes (T2D)  | Baseline           | 213                 | 0.30 (0.10,0.70)   | 210                 | 0.30 (0.10,1.00)   | 211                 | 0.30 (0.10,0.90)   |                        |                        |                        |
|                  | Change to week 144 | 129                 | +1.50 (0.50, 3.50) | 131                 | +0.80 (0.30, 2.60) | 114                 | +1.25 (0.40, 3.40) | 0.674                  | 0.024                  | 0.048                  |

Risk score given as median change (Q1, Q3) in score from baseline. Risk score gives 10-year risk (%) of developing an incident CVD or T2D event. P-values were derived from Mann-Whitney U tests comparing two different treatment groups.

## 518 RISK FACTORS FOR PROGRESSION FROM PREDIABETES TO DIABETES IN PERSONS WITH HIV

Mary Clare C. Masters<sup>1</sup>, Yajing Bao<sup>2</sup>, Katherine Tassiopoulos<sup>2</sup>, Jingyan Yang<sup>3</sup>, E. Turner Overton<sup>4</sup>, Scott Letendre<sup>5</sup>, Todd Brown<sup>6</sup>, Frank Palella<sup>1</sup>, Kristine Erlandson<sup>7</sup>  
<sup>1</sup>Northwestern University, Chicago, IL, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Columbia University, New York, NY, USA, <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>5</sup>University of California San Diego, San Diego, CA, USA, <sup>6</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>7</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA

**Background:** Persons with HIV (PWH) experience increased incidence and prevalence of diabetes mellitus (DM) compared to the general population. However, risk factors associated with progression from pre-DM to DM for PWH on modern antiretroviral therapy (ART) regimens have not been fully characterized.

**Methods:** AIDS Clinical Trials Group (ACTG) A5322 (HAILO) is an observational cohort study of PWH ≥40 years old being followed for ascertainment of clinical outcomes associated with HIV, ART and aging. All participants initiated ART through an ACTG randomized clinical trial and were subsequently followed in the observational study ACTG A5000/ALLRT prior to being followed in HAILO. We used proportional hazards Cox regression models to identify risk factors for development of DM among PWH with pre-DM diagnosed either at ALLRT entry (baseline) or during follow-up in ALLRT or HAILO. Pre-DM was defined as fasting blood glucose (FBG) of 100-125 mg/dl and DM as FBG ≥126 mg/dl, treatment of diabetes, or clinical diagnosis. Factors associated with DM (p-value <0.10) in univariable models were included in a multivariable model.

**Results:** Among 1035 HAILO participants, 60 (6%) had DM and 74 (7%) had pre-DM at baseline. Another 679 (66%) developed pre-DM during follow-up. Of the 753 participants with pre-DM, 167 (22%) subsequently developed DM; median (IQR) time to DM was 45.3 weeks (18.7, 58.6). In a multivariable model (Table), the risk of developing DM among those with pre-DM increased with higher BMI at pre-DM diagnosis. InSTI use (12% of participants) at or prior to pre-DM and CD4 count >200 copies/mm<sup>3</sup> at pre-DM diagnosis were associated with a lower risk of developing DM. In a separate multivariable model with waist circumference replacing BMI, each 1-unit increase was associated with a 3% increased risk of developing DM (HR=1.03, 95%CI=1.01, 1.04; p<0.01).

**Conclusion:** Though InSTI use has been associated with weight gain, its use was associated with a lower risk of progression to DM in this cohort. Higher CD4 was also associated with a lower risk of progression to DM, suggesting that immunosenescence and inflammation may be mediators in DM development among PWH with pre-DM. Further characterization of the metabolic effects of InSTI use and the effects of immune activation and inflammation on development of DM in PWH is needed.

Table. Clinical and demographic factors and risk of progression to diabetes among those with prediabetes (N=753)

| Variable  |           | HR   | 95% CI     | p-value |
|---|-----------|------|------------|---------|
| Clinical site region (ref=West)                       | Northeast | 1.68 | 1.09, 2.61 | 0.02    |
|   | Midwest   | 1.40 | 0.91, 2.16 | 0.13    |
|   | South     | 1.19 | 0.72, 1.95 | 0.50    |
| HIV-1 RNA <50 (copies/ml) <sup>1</sup>                |           | 0.95 | 0.68, 1.32 | 0.74    |
| CD4 counts (cells/mm <sup>3</sup> ) >200 <sup>1</sup> |           | 0.55 | 0.37, 0.81 | <0.01   |
| BMI, per 1 unit increase <sup>1</sup>                 |           | 1.05 | 1.02, 1.08 | <0.01   |
| INSTI-containing regimen <sup>2</sup>                 |           | 0.21 | 0.07, 0.67 | <0.01   |
| Family history of CVD                                 |           | 0.83 | 0.53, 1.28 | 0.40    |
| History of hypertension <sup>3</sup>                  |           | 1.24 | 0.87, 1.77 | 0.24    |

<sup>1</sup>At diagnosis of pre-diabetes  
<sup>2</sup>At or before diagnosis of pre-diabetes. Of those on an INSTI-containing regimen, 67% were on raltegravir, 18% dolutegravir, 12% elvitegravir, and 3% bictegravir.  
<sup>3</sup>All variables in table were associated with risk of DM in univariable models (p<0.10)

**519 HYPERGLYCEMIA AND DIABETES MELLITUS IN PERSONS LIVING WITH AND WITHOUT HIV IN AFRICOS**

**David Chang**<sup>1</sup>, Allahna Esber<sup>1</sup>, Nicole Dear<sup>1</sup>, Michael Iroezindu<sup>1</sup>, Isaac Tsikhutsu<sup>2</sup>, Valentine Singoei<sup>1</sup>, Hannah Kibuuka<sup>3</sup>, Emmanuel Bahemana<sup>1</sup>, Trevor A. Crowell<sup>1</sup>, Christina Polyak<sup>1</sup>, Julie Ake<sup>1</sup>, Catherine Godfrey<sup>4</sup>

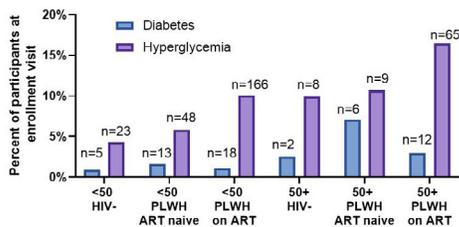
<sup>1</sup>US Military HIV Research Program, Silver Spring, MD, USA, <sup>2</sup>Kenya Medical Research Institute, Nairobi, Kenya, <sup>3</sup>Aalborg University Hospital, Aalborg, Denmark, <sup>4</sup>Office of the Global AIDS Coordinator, Washington, DC, USA

**Background:** Diabetes mellitus (DM) and hyperglycemia are prevalent in persons living with HIV (PLWH) in high income countries and are more common with an aging cohort. Little data on their prevalence is available in Africa especially in PLWH over 50, a growing population of individuals on treatment. There are also concerns about development of hyperglycemia with antiretroviral therapy (ART), particularly with dolutegravir (DTG). We examined differences in prevalence of DM and hyperglycemia in an ongoing African Cohort study.

**Methods:** The African Cohort Study (AFRICOS) is a prospective cohort enrolling adults with and without HIV at 12 clinical sites in Kenya, Tanzania, Uganda and Nigeria. Data were collected from January 2013 to September 2020 evaluating prevalence and incidence of DM and hyperglycemia. DM was defined as a fasting glucose >126 mg/dL or receipt of medication for DM and hyperglycemia was defined as fasting glucose >99 mg/dL, nonfasting > 199 mg/dL or medication. Multivariable logistic regression with generalized estimating equations was used to estimate odds ratios (OR) and 95% confidence intervals (CIs) for factors associated with diabetes and hyperglycemia.

**Results:** There were a total of 3568 participants, 1493(41.8%) males and 2075(58.2%) females. PLWH comprised 2949(82.7%), and 619(17.3%) without HIV. 560(15.7%) were age >50. At enrollment there was a statistically significant difference in prevalence of DM and hyperglycemia by HIV status and age. PLWH age >50 and on ART had the highest prevalence of hyperglycemia (16%), ART naïve PLWH age >50 had the highest prevalence of DM (7%, Figure). After adjustment for sex and study site, PLWH age 50+ had 5.29 the odds of having DM (95% CI: 2.61-10.70) and 86% increased odds of hyperglycemia (95% CI: 1.38-2.50) at all visits compared to people without HIV age 50. DM incidence did not vary by HIV and ART status including receipt, of DTG. Incidence of hyperglycemia was higher in PLWH <50.

**Conclusion:** In this African cohort, hyperglycemia and diabetes were more commonly seen in PLWH than persons without HIV especially those over 50. There was a higher incidence of hyperglycemia in the PLWH <50 compared to those without HIV. HIV and age >50 did not pose a significant risk for incident diabetes although this is likely limited by the sample size. As DTG use becomes more common, trends in DM and hyperglycemia need further evaluation.



among persons with HIV (PWH) have a heavy male preponderance. We assessed gender as a factor impacting the association between T2DM and HIV in the United States.

**Methods:** A cross-sectional study using a multi-health system electronic medical record analytics platform was performed (Explorys; IBM Watson Health, Cambridge, MA, USA). The database contains 64 million persons, representing 15% of the population across all 4 census regions of the United States. Persons with all types of insurance including self-pay are represented. All adults active in the database between Nov 2015 and Nov 2020 with complete records on age, gender, race and body mass index were included. PWH were identified using ICD-9 or ICD-10 codes related to HIV AND prescription for antiretroviral therapy. T2DM was defined using SNOMED-CT terms that corresponded to ICD 9 or 10 codes 250.x0-x2 and E11.8, respectively. Comparisons between groups were performed using the chi-square test with a P-value ≤0.05 being considered statistically significant.

**Results:** We identified 39,500 PWH and 13,015,560 HIV-seronegative controls. PWH were mostly younger than 60 years of age (29,260, 74%), 74% were male and 26% were female. Women with HIV (WWH) were more likely to be black and obese compared to men with HIV (MWH) (p<0.001). Prevalence of T2DM was higher among WWH compared to HIV-seronegative women (22% vs 14%, p<0.001). WWH were more likely to have T2DM across all age-subgroups (Figure 1). The prevalence of T2DM among MWH was lower compared to HIV-seronegative controls (16% vs 17%, p<0.002).

**Conclusion:** In this large US population-based study, we demonstrate that gender is a defining factor when considering the association between HIV and T2DM. WWH are disproportionately affected by T2DM with early data suggesting this could be due to higher rates of obesity. HIV-related clinical studies on metabolic risk should ensure adequate enrollment of WWH to take account of the differential risk for T2DM.

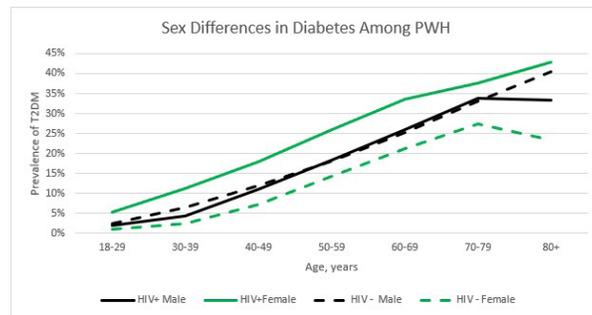


Figure 1: Sex Differences in Type 2 Diabetes Mellitus Prevalence among Persons with HIV

**521 MITOCHONDRIAL DNA HAPLOGROUPS AND RISK OF DIABETES IN VETERANS WITH AND WITHOUT HIV**

**Todd Hulgan**<sup>1</sup>, Suman Kundu<sup>1</sup>, David Samuels<sup>2</sup>, Samuel Bailin<sup>1</sup>, Ke Xu<sup>3</sup>, Kaku So-Armah<sup>4</sup>, Adeel Butt<sup>5</sup>, Mariana Gerschenson<sup>6</sup>, Matthew Goetz<sup>7</sup>, Russell Tracy<sup>8</sup>, Vincent Marconi<sup>9</sup>, Amy Justice<sup>10</sup>, Matthew Freiberg<sup>1</sup>, John Koethe<sup>1</sup>

<sup>1</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>2</sup>Vanderbilt University, Nashville, TN, USA, <sup>3</sup>Yale University, New Haven, CT, USA, <sup>4</sup>Boston University, Boston, MA, USA, <sup>5</sup>Weill Cornell Medicine, New York, NY, USA, <sup>6</sup>University of Hawaii at Manoa, Honolulu, HI, USA, <sup>7</sup>VA Greater Los Angeles Health Care System, Los Angeles, CA, USA, <sup>8</sup>University of Vermont, Burlington, VT, USA, <sup>9</sup>Atlanta VA Medical Center, Decatur, GA, USA, <sup>10</sup>VA Connecticut Healthcare System, West Haven, CT, USA

**Background:** Type 2 diabetes mellitus (DM) is common in persons with HIV. Immune activation, senescence, and mitochondrial dysfunction may contribute to DM risk. We have previously shown that DM risk differed by mitochondrial DNA (mtDNA) haplogroups in women of African ancestry with HIV. We sought to examine haplogroup associations with DM risk and available T cell phenotypes among persons with and without HIV in the Veterans Aging Cohort Study (VACS) Biomarker Cohort.

**Methods:** VACS participants had DM outcomes determined by an algorithm including lab values, medications, and diagnosis codes. mtDNA haplogroups were derived from genome-wide genotyping and HaploGrep. Analyses included logistic regression of prevalent DM and Cox regression of incident DM, stratified by self-reported ancestry and HIV status. T cell phenotypes were determined from flow cytometry of cryopreserved peripheral blood mononuclear cells. Covariates in adjusted models included age, body mass index, hazardous

**520 SEX DIFFERENCES IN DIABETES PREVALANCE AMONG PERSONS WITH HIV IN THE UNITED STATES**

**Morgan Birabaharan**<sup>1</sup>, David Kaelber<sup>2</sup>, Thomas Martin<sup>1</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>Case Western Reserve University, Cleveland, OH, USA

**Background:** There is conflicting evidence for an association between type 2 diabetes mellitus (T2DM) and HIV. Notably, most studies of T2DM prevalence

drinking status, HCV status, CD4+ T cell count, and plasma HIV RNA level at VACS entry, and selected T-cell phenotype markers. Prevalent DM cases were excluded from incidence analyses.

**Results:** A total of 2019 Veterans (65% with HIV) had mtDNA haplogroups, DM outcomes, and T cell phenotyping. The majority were non-Hispanic Black (68%) and male (95%); 21% had prevalent DM and there were 202 cases of incident DM over a median of >8 years of follow-up. Among 781 Black Veterans with HIV and no prevalent DM, mtDNA haplogroup L3 (N=313) was associated with incident DM (HR 1.6; 95% CI 1.1-2.5) adjusting for the factors above and percent senescent (CD28-) CD4+ T cells, which were lower in Black Veterans having haplogroup L3 vs. other African haplogroups (median 13% vs. 15%; Wilcoxon  $p=0.03$ ). No European or other African haplogroups were associated with prevalent or incident DM, and there were no statistically significant associations in Veterans without HIV.

**Conclusion:** A common mtDNA haplogroup was associated with incident DM in non-Hispanic Black Veterans with HIV. This haplogroup was also associated with DM risk in a prior study of Black women with HIV. While the VACS is large, the number without HIV and individual haplogroups were small, and incident DM cases were relatively few. Haplogroup L3 was also associated with less senescent CD4+ T cells in peripheral blood, but this may not be the primary driver of its relationship with DM. Further study is needed to characterize biologic effects of haplogroup L3 that may confer DM risk.

## 522 RELATIONSHIP OF T-CELL MITOCHONDRIAL GENE EXPRESSION AND DIABETES IN PERSONS WITH HIV

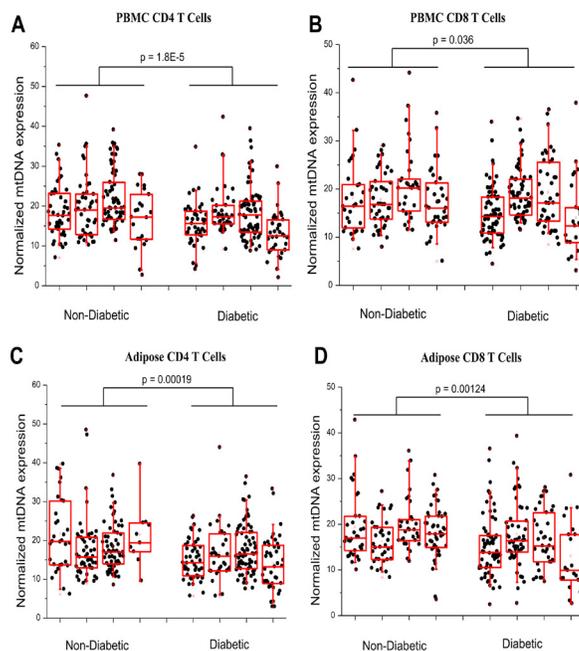
Samuel Bailin<sup>1</sup>, Todd Hulgan<sup>1</sup>, Celestine Wanjalla<sup>1</sup>, John Koethe<sup>1</sup>, David Samuels<sup>2</sup>  
<sup>1</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>2</sup>Vanderbilt University, Nashville, TN, USA

**Background:** Metabolic diseases including type 2 diabetes mellitus (T2DM) are common in persons living with HIV (PLWH). Studies have found reduced mitochondrial DNA (mtDNA) copy number in peripheral blood mononuclear cells (PBMCs) is associated with T2DM in the general population. Single cell RNA sequencing (scRNA-seq) offers a promising method to study mtDNA expression at the cellular level. We hypothesized that PLWH and T2DM will have reduced mtDNA gene expression in T cells from PBMC and adipose tissue compared with PLWH without T2DM.

**Methods:** Four diabetic and 4 non-diabetic PLWH from a larger cohort who were on antiretroviral therapy for at least 18 months with viral suppression (<50 copies/mL) for at least 12 months underwent PBMC collection and subcutaneous abdominal tissue liposuction. Samples were stained and underwent flow cytometry for phenotyping and single cell sorting. Well-specific barcodes were used to generate single-cell cDNA libraries followed by 3' and 5' amplification. Paired-end reads were sequenced using Illumina NextSeq and reads were then aligned to the GRCh38 human reference genome. Thirteen mtDNA coding genes were identified and average gene expression was calculated and normalized as a ratio of overall gene expression. Normalized mtDNA expression in diabetics was compared with non-diabetics using the Student's t-test in PBMC and adipose tissue separately.

**Results:** Diabetic and non-diabetic individuals did not differ significantly by age or body mass index. The average normalized mtDNA expression was lower among individuals with T2DM compared with individuals without T2DM in CD4+ (16.8 vs 19.9;  $p<0.001$ ; Figure 1A) and CD8+ (17.0 vs 18.5;  $p=0.04$ ; Figure 1B) T cells from PBMC. Similarly, in subcutaneous abdominal tissue mtDNA expression was lower among individuals with T2DM compared with individuals without T2DM in CD4+ (16.1 vs 19.0;  $p<0.001$ ; Figure 1C) and CD8+ (16.0 vs 18.4;  $p<0.001$ ; Figure 1D) T cells. Average mtDNA expression in CD8 and CD4 T cells was highly correlated across all individuals in PBMCs ( $R^2=0.86$ ,  $p=8.8E-4$ ) and in adipose tissue ( $R^2=0.66$ ,  $p=0.014$ ).

**Conclusion:** PLWH who have T2DM have reduced single cell mtDNA gene expression compared to those without T2DM in both circulating and subcutaneous adipose tissue CD4+ and CD8+ T cells. We use scRNA-seq to show an important link between mtDNA expression and T2DM. Future studies with longitudinal follow up and larger sample sizes are needed to confirm these findings.



**Figure 1.** Normalized mtDNA expression plotted for each cell by individual. The average normalized mtDNA expression was compared between non-diabetic and diabetic individuals for peripheral blood mononuclear cells (PBMC) CD4 T cells (A) PBMC CD8 T cells (B) adipose tissue CD4 T cells (C) and adipose tissue CD8 T cells (D).

## 523 CD4+ T EFFECTOR MEMORY CD45RA+ CELLS ARE ASSOCIATED WITH DIABETES IN PERSONS WITH HIV

Samuel Bailin<sup>1</sup>, Suman Kundu<sup>1</sup>, Melissa Wellons<sup>1</sup>, Matthew Freiberg<sup>1</sup>, Margaret Doyle<sup>2</sup>, Russell Tracy<sup>2</sup>, Amy Justice<sup>3</sup>, Kaku So-Armah<sup>4</sup>, Celestine Wanjalla<sup>1</sup>, Alan Landay<sup>5</sup>, Simon Mallal<sup>1</sup>, John Koethe<sup>1</sup>  
<sup>1</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>2</sup>University of Vermont, Burlington, VT, USA, <sup>3</sup>VA Connecticut Healthcare System, West Haven, CT, USA, <sup>4</sup>Boston University, Boston, MA, USA, <sup>5</sup>Rush University Medical Center, Chicago, IL, USA

**Background:** Changes in the distribution of T cell subsets have been linked to prevalent diabetes in the general population. As persistent immune activation is a hallmark of HIV infection, we assessed whether T cell subsets were associated with incident diabetes in persons with HIV (PWH).

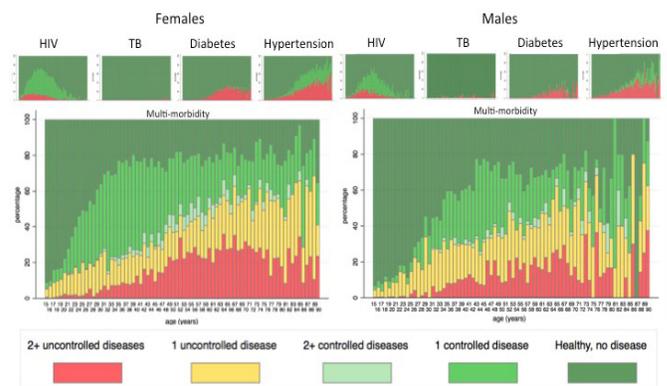
**Methods:** We performed flow cytometry and functional assays on peripheral blood mononuclear cells collected from PWH and HIV-negative participants in the Veterans Aging Cohort Study between 2005 and 2007 to characterize CD4+ and CD8+ memory (central, effector, and effector RA+ [TEMRA]), CD57+, CD28-, and TH1, TH2, and TH17 CD4+ T cells. We used two definitions of TEMRA cells: CD45RA+CD28-CD57+ (TEMRA1) and CD45RA+CD27- (TEMRA2) (Table 1). Cases of incident diabetes were identified by two-physician chart adjudication. Individuals were followed until the onset of diabetes, death or end of study. We assessed PWH and HIV-negative participants separately using multivariable Cox proportional hazards models with T cell subset as the main exposure adjusted for demographic variables, lipid levels, cytomegalovirus (CMV) and hepatitis c virus serostatus, alcohol use, circulating inflammatory markers, and viral load and antiretroviral therapy use (PWH only). We report the hazard ratio (HR) for incident diabetes per standard deviation increment in the T cell subset.

**Results:** A total of 1259 PWH and 578 HIV-negative individuals were without diabetes at baseline and there were 238 incident diabetes events (133 [10.6%] in PWH and 105 [18.2%] in HIV-negative) over a median follow-up time of 8.6 years. The median age was 52 years, 69% were black, 95% were male, and 65% of PWH were virologically suppressed. In the adjusted model, a higher baseline proportion of CD4+ TEMRA cells, using both definitions, was associated with increased risk of incident diabetes in PWH only (TEMRA1 HR 1.16 [1.00,1.34];  $p=0.05$  and TEMRA2 HR 1.20 [1.04,1.38];  $p=0.01$ ) (Table 1). Higher proportion of CD4+ CD28- T cells approached significance in the model (HR 1.16 [0.99,1.36];  $p=0.06$ ) in PWH only. A similar association was not observed for CD8+ TEMRA cells, and no T cell subsets were associated with risk of incident diabetes in HIV-negative individuals.

**Conclusion:** Higher baseline proportion of CD4+, but not CD8+, TEMRA cells was associated with an increased risk of incident diabetes in PWH. As diabetes is common in PWH, understanding the potential role of T cells may provide insight into prevention or therapeutic strategies.

**Table 1.** Multivariable Cox proportional hazards models, stratified by HIV status, assessing the relationship of baseline T cell subsets and incident diabetes adjusted for age, race, cytomegalovirus serostatus, viral load and antiretroviral therapy use (persons with HIV only), high-density lipoprotein, low-density lipoprotein, total cholesterol, time updated body mass index, hepatitis C virus serostatus, history of alcohol abuse, and circulating concentrations of interleukin-6, D-dimer, and soluble CD14. CI, confidence interval; SD, standard deviation; T<sub>EMRA</sub>, T effector memory RA\*

|   | HIV-negative (N = 578)                 |         | Persons with HIV (N = 1259)            |         |
|---|--|---------|--|---------|
|   | Hazard Ratio per SD Increment (95% CI) | P value | Hazard Ratio per SD Increment (95% CI) | P value |
| <b>CD4<sup>+</sup> T cell subset</b>  |  |         |  |         |
| CD4 <sup>+</sup> CD45RA <sup>+</sup> CD28 <sup>+</sup> CD57 <sup>+</sup> (T <sub>EMRA</sub> ) | 1.06 [0.77, 1.44]                      | 0.73    | 1.16 [1.00, 1.34]                      | 0.05    |
| CD4 <sup>+</sup> CD45RA <sup>+</sup> CD27 <sup>+</sup> (T <sub>H1RA2</sub> )                  | 1.10 [0.93, 1.30]                      | 0.27    | 1.20 [1.04, 1.38]                      | 0.01    |
| CD4 <sup>+</sup> CD28 <sup>+</sup>  | 1.03 [0.76, 1.40]                      | 0.86    | 1.16 [0.99, 1.36]                      | 0.06    |
| CD4 <sup>+</sup> CD57 <sup>+</sup> CD28 <sup>+</sup>  | 1.01 [0.87, 1.18]                      | 0.85    | 0.96 [0.84, 1.09]                      | 0.52    |
| <b>CD8<sup>+</sup> T cell subset</b>  |  |         |  |         |
| CD8 <sup>+</sup> CD45RA <sup>+</sup> CD28 <sup>+</sup> CD57 <sup>+</sup> (T <sub>EMRA</sub> ) | 0.88 [0.73, 1.07]                      | 0.21    | 1.08 [0.91, 1.29]                      | 0.37    |
| CD8 <sup>+</sup> CD45RA <sup>+</sup> CD27 <sup>+</sup> (T <sub>H1RA2</sub> )                  | 0.82 [0.67, 1.01]                      | 0.06    | 1.13 [0.96, 1.33]                      | 0.15    |
| CD8 <sup>+</sup> CD28 <sup>+</sup>  | 0.87 [0.70, 1.08]                      | 0.22    | 0.99 [0.83, 1.18]                      | 0.90    |
| CD8 <sup>+</sup> CD57 <sup>+</sup> CD28 <sup>+</sup>  | 1.04 [0.89, 1.22]                      | 0.60    | 1.00 [0.86, 1.16]                      | 0.98    |



**524 CONVERGENCE OF INFECTIOUS AND NONCOMMUNICABLE DISEASES IN RURAL SOUTH AFRICA**

**Emily B. Wong<sup>1</sup>**, Stephen Olivier<sup>1</sup>, Resign Gunda<sup>1</sup>, Olivier Koole<sup>1</sup>, Kathy Baisley<sup>2</sup>, Diego Cuadros<sup>3</sup>, Frank Tanser<sup>1</sup>, Alison D. Grant<sup>2</sup>, Kobus Herbst<sup>1</sup>, Janet Seeley<sup>1</sup>, Willem A. Hanekom<sup>1</sup>, Thumbi Ndung'u<sup>1</sup>, Mark Siedner<sup>1</sup>, Deenan Pillay<sup>1</sup>, for the Vukuzazi Team

<sup>1</sup>Africa Health Research Institute, Mtubatuba, South Africa, <sup>2</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>3</sup>University of Cincinnati, Cincinnati, OH, USA

**Background:** There has been remarkable progress in the treatment of HIV throughout sub-Saharan Africa but data are limited on the prevalence and overlap of other significant causes of disease in HIV-endemic populations.

**Methods:** In a rural district of South Africa, we leveraged demographic and health surveillance infrastructure to estimate the population prevalence and geospatial distribution of HIV, active and lifetime tuberculosis, elevated blood glucose, elevated blood pressure and combinations of these. Adolescent and adult residents were offered multi-disease screening at mobile health camps near their homes. The health screening included WHO-STEP protocols for anthropomorphic and blood pressure measurements, HIV Ag–Ab enzyme immunoassay, HIV viral load and CD4 count, glycosylated hemoglobin (HbA1c) and TB screening (digital chest x-ray with automated image interpretation (CAD4TB), sputum Xpert MTB/RIF Ultra and liquid mycobacterial culture).

**Results:** 17,118 adolescents and adults were assessed. Overall, 52.1% (95%CI 51.3–52.9) had at least one active disease: 34.2% (95%CI 33.5–34.9) had HIV, 1.4% (95%CI 1.2–1.6) had active tuberculosis, 21.8% (95%CI 21.2–22.4) had lifetime tuberculosis, 8.5% (95%CI 8.1–8.9) had elevated blood glucose and 23.0% (95%CI 22.4–23.6) had elevated blood pressure. Appropriate treatment and control of disease was highest for HIV (76.3%), and lower for elevated blood pressure (40.0%), active tuberculosis (31.3%) and elevated blood glucose (6.9%). Disease prevalence differed significantly by sex, across age groups and geospatially: men had higher prevalence of active and lifetime tuberculosis, while women had extremely high prevalence of HIV in middle age and increasing prevalence of multiple and poorly controlled non-communicable diseases after the age of 50 years.

**Conclusion:** We found a convergence of infectious and non-communicable disease epidemics in a rural South African population, with HIV relatively well treated, but tuberculosis, elevated blood glucose and elevated blood pressure poorly diagnosed and treated. A public health response that expands the successes of HIV testing and treatment programme to provide multi-disease differentiated care targeted to specific populations is required to optimize health in such settings in sub-Saharan Africa.

**525 COMORBIDITY BURDEN IN PEOPLE LIVING WITH HIV IN THE UNITED STATES**

**Misti L. Paudel<sup>1</sup>**, Girish Prajapati<sup>2</sup>, Erin K. Buysman<sup>1</sup>, Swarnali Goswami<sup>2</sup>, Jianbin Mao<sup>3</sup>, Kimberly McNiff<sup>1</sup>, Princy N. Kumar<sup>3</sup>

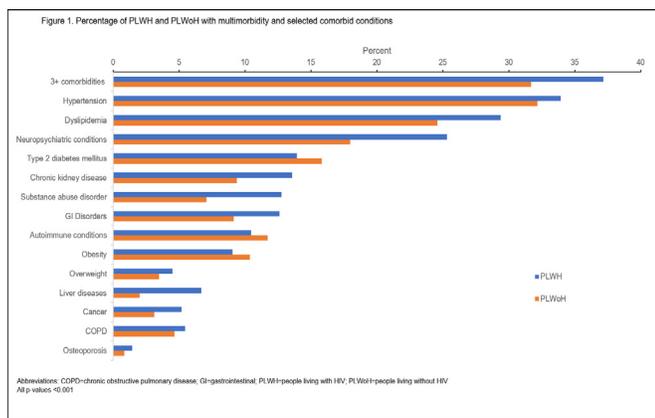
<sup>1</sup>Optum, Eden Prairie, MN, USA, <sup>2</sup>Merck & Co, Inc, Kenilworth, NJ, USA, <sup>3</sup>Georgetown University Medical Center, Washington, DC, USA

**Background:** Antiretroviral (ARV) therapy is required life-long among people living with HIV (PLWH). It is important to understand the burden of comorbidities and comedications in PLWH to optimize clinical care.

**Methods:** Retrospective analyses of administrative claims data for commercial and Medicare Advantage enrollees from the Optum Research Database was conducted. PLWH cohort included adults (≥18 years) with ≥1 pharmacy claim for an ARV drug or HIV/AIDS diagnosis code in medical claims in 2018 calendar year (index date: earliest of pharmacy or HIV diagnosis claim date). Comparison cohort included adults without HIV (PLWoH), matched 2:1 with PLWH on age, gender, race, region and insurance type. Continuous health plan enrollment of 12 months (baseline) prior to, and 30 days (follow-up) after index date was required. Comorbidities were identified during baseline using ICD-9/10 diagnosis codes from medical claims. Charlson Comorbidity Index (CCI) was computed excluding HIV/AIDS. Baseline comedications were identified from pharmacy/medical claims using National Drug Codes. Differences in PLWH vs PLWoH accounted for the matched design and used a Z-test with robust errors for continuous variables and Rao-Scott test for categorical variables.

**Results:** A total of 20,256 PLWH and 40,512 matched PLWoH were analyzed. The mean age was 52 years, 80% were male, 46% were White, and 59% resided in South. 17,694 (87%) PLWH received ARV treatment (NRTI=94%; INStI=63%; NNRTI=29%; PI=17%). Hypertension was the most common comorbidity followed by dyslipidemia and neuropsychiatric conditions in both PLWH and PLWoH. Presence of ≥3 comorbidities (Figure 1), and mean CCI were higher in PLWH than PLWoH (0.93 vs 0.61, p<0.001), respectively. Most comorbid conditions were more prevalent among PLWH compared to PLWoH except obesity, type 2 diabetes mellitus, and autoimmune disorders which were more common in PLWoH (all p<0.01). Polypharmacy (≥5 medications) was more prevalent among PLWH vs PLWoH (84% vs 61%, p<0.001). The most prevalent non-ARV comedications in PLWH vs PLWoH were cardiovascular medications, 47% vs 42%; antidepressants, 27% vs 18%; and chronic antibiotics, 15% vs 7%; respectively (all p<0.001).

**Conclusion:** Multimorbidity and polypharmacy were more prevalent in PLWH compared to matched PLWoH. The study findings suggest the need for clinicians to consider comorbidities and comedications when selecting ARV regimens to minimize drug interactions and adverse events and thereby improve patient outcomes.



## 526 HIV DIFFERENTIALLY IMPACTS AGE-RELATED COMORBIDITY BURDEN AMONG US WOMEN AND MEN

Lauren F. Collins<sup>1</sup>, Frank Paella<sup>2</sup>, Cyra C. Mehta<sup>1</sup>, JaNae Holloway<sup>1</sup>, Valentina Stosor<sup>2</sup>, Jordan Lake<sup>3</sup>, Todd Brown<sup>4</sup>, Kathryn Anastos<sup>5</sup>, Seble Kassaye<sup>6</sup>, Adaora Adimora<sup>7</sup>, Mirjam-Colette Kempf<sup>8</sup>, Susan L. Koletar<sup>9</sup>, Phyllis Tien<sup>10</sup>, Igbo Ofotokun<sup>1</sup>, Anandi N. Sheth<sup>1</sup>

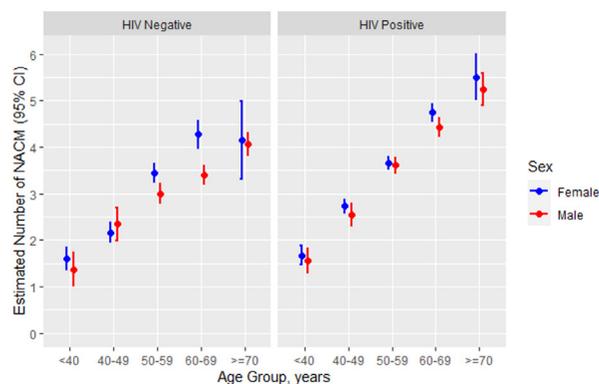
<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Northwestern University, Chicago, IL, USA, <sup>3</sup>University of Texas at Houston, Houston, TX, USA, <sup>4</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>5</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>6</sup>Georgetown University, Washington, DC, USA, <sup>7</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>8</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>9</sup>The Ohio State University, Columbus, OH, USA, <sup>10</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** Age-related non-AIDS comorbidities (NACM) occur earlier and more frequently among people with HIV (PWH) than HIV-negative (HIV-) peers. HIV may also differentially impact the burden of NACM experienced by women vs men.

**Methods:** PWH and HIV- participants followed in the MACS/WIHS Combined Cohort Study (MWCCS) since 2008/2009 (when >80% of male/female participants used antiretroviral therapy) were included with outcomes measured up to 03/2019. Age, covariates, NACM prevalence, and NACM burden (total number out of 10) were summarized as of last observation. Unadjusted and adjusted (race, body mass index [BMI], smoking, drinking, crack/cocaine, socioeconomic status) linear regression models assessed the effects of HIV serostatus, age and sex on NACM burden.

**Results:** Women (2316 PWH, 922 HIV-) vs men (1452 PWH, 1239 HIV-) had a median age of 51 vs 58 years, median BMI of 30 vs 26 kg/m<sup>2</sup>, 65% vs 25% were Black, and 78% vs 32% had income <150% of the federal poverty level, respectively. Overall, individual NACM prevalence ranged from 9-71%, and the distribution for women/men was: hypertension (68%/75%), psychiatric illness (55%/58%), dyslipidemia (41%/64%), liver (34%/38%), bone (42%/19%), lung (38%/10%) disease, diabetes (24%/17%), cardiovascular (15%/15%), kidney (14%/15%) disease, and cancer (7%/12%). Mean NACM burden was higher among women vs men (3.4 vs 3.2,  $p=0.015$ ). In the unadjusted model, the estimated mean difference in NACM burden was significantly greater for women vs men in every age strata among PWH (all  $p<0.05$ ): +0.33 (<40y), +0.37 (40-49y), +0.38 (50-59y), +0.66 (60-69y), +0.62 ( $\geq 70y$ ); however, differed for women vs men by age strata among HIV- participants: +0.52 (<40y,  $p=0.01$ ), -0.07 (40-49y,  $p=0.72$ ), +0.88 (50-59y,  $p<0.01$ ), +1.39 (60-69y,  $p<0.01$ ), +0.33 ( $\geq 70y$ ,  $p=0.46$ ) [HIV\*age\*sex interaction,  $p<0.01$ ]. In the adjusted model, findings were attenuated but HIV and age still significantly modified the estimated NACM burden by sex (HIV\*age\*sex interaction,  $p=0.038$ , Figure).

**Conclusion:** The prevalence and burden of NACM was high in the MWCCS among men and women with or at-risk for HIV, particularly for hypertension, psychiatric illness, dyslipidemia, liver, and bone disease. NACM burden was higher in women vs men, particularly among PWH, and the distribution of specific NACM prevalence differed by sex. Given HIV is associated with differential effects on age-related comorbidities by sex, HIV serostatus- and sex-specific strategies for NACM screening and prevention are needed.



**Figure.** Estimated mean number of NACM among persons with HIV and HIV-negative participants in the MACS/WIHS Combined Cohort Study, stratified by sex and age group, adjusted for covariates (BMI, SES, crack/cocaine use, smoking status, alcohol use, race/ethnicity) (HIV\*age\*sex interaction term,  $p=0.038$ ).

## 527 EFFECTS OF SWITCH FROM 3DR TO 2DR ON INFLAMMATORY BIOMARKERS

Sergio Serrano-Villar<sup>1</sup>, María Rosa López-Huertas<sup>2</sup>, Daniel Jiménez<sup>1</sup>, Javier Martínez-Sanz<sup>1</sup>, Raquel Ron<sup>3</sup>, Luis Fernando López Cortés<sup>4</sup>, José-Ramón Blanco<sup>5</sup>, Victor Asensi<sup>6</sup>, David Dalmau<sup>7</sup>, María José Galindo<sup>8</sup>, Santiago Moreno<sup>1</sup>, for the Spanish AIDS Research Network (CORIS)

<sup>1</sup>Hospital Ramón y Cajal, Madrid, Spain, <sup>2</sup>Institute of Health Carlos III, Madrid, Spain, <sup>3</sup>UCL Great Ormond Street Institute of Child Health, London, UK, <sup>4</sup>Hospital Universitario Virgen del Rocío, Sevilla, Spain, <sup>5</sup>Hospital San Pedro, La Rioja, Spain, <sup>6</sup>Hospital Universitario Central de Asturias, Oviedo, Spain, <sup>7</sup>Hospital Universitari Mútua de Terrassa, Terrassa, Spain, <sup>8</sup>Hospital Clinic de Valencia, Valencia, Spain

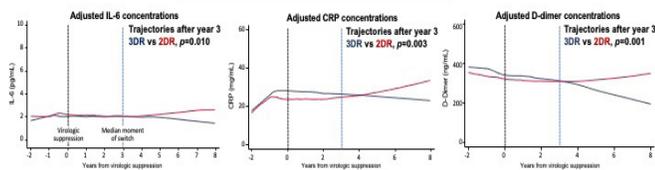
**Background:** Because inflammation has been linked to HIV transcription in lymphoid tissues during ART-mediated viral suppression (VS), it is necessary to address the long-term effects of changing triple therapy (3DR) to 2-drug regimens (2DR) on plasma inflammatory markers.

**Methods:** Nested study in the Spanish AIDS Research Network (CoRIS). We selected HIV-infected ART-naive patients initiating 3DR from 2004 to 2017 who achieved VS in the first 48 weeks of ART and either remained on 3DR during their entire follow-up or were switched to 2DR (3TC+bPI; 3TC+DTG; DTG+RPV) after at least 48 weeks of suppressive ART. 180 subjects were selected based on plasma availability and longer follow-up. We assessed the trajectories of inflammation markers (IL-6, hsCRP), macrophage activation (sCD163), monocyte activation (sCD14), coagulation (D-dimer) and markers of intestinal damage (IFABP) during VS using multivariate piecewise mixed models.

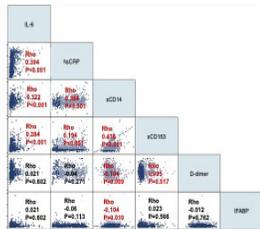
**Results:** We analyzed 619 plasma samples from 148 subjects (3DR, N=90; 2DR, N=58), mean age 38 (SD 10) years, 87% men, 67% MSM, mean CD4 nadir 278 (SD 185) cells/uL, median duration of VS 4.3 (3-6.2) years. Median time from ART initiation to censoring was 4.6 (3.2-6.2) years. Median time from VS to 2DR was 3.4 (1.8-5.2) years. Subjects with 3DR experienced a slow decline of IL6, CRP, sCD14, sCD163 and D-dimers over time (figure A). In contrast, compared to 3DR, switching to 2DR was associated with increases in IL-6 ( $p=0.01$ ), CRP ( $p=0.003$ ) and D-dimer ( $p=0.001$ ) after year 3 from VS, after adjusting for covariates. Compared to 3DR, 2DR was associated with higher risk of CRP quartile increase (aOR 3.3, 95%CI 1.1-10) and D-dimer quartile increase (aOR 3.7, 95%CI 1.1-13). The adjusted biomarker trajectories did not reveal a distinct pattern according to the type of 2DR used. We also studied cross-correlations among the biomarkers, and found sCD14 and sCD163 to be more highly correlated (figure B,  $Rho$  0.438,  $P<0.0001$ ).

**Conclusion:** In this observational study in virally suppressed individuals, maintaining 3DR was associated with a more favourable long-term anti-inflammatory profile than switching to 2DR. The potential clinical implications of these findings on the development of non-AIDS events deserve further investigation.

**A. Piecewise Linear Mixed Models for IL-6, CRP and D-dimer**



**B. Crossed-correlations between inflammatory biomarkers**



**Table 1: Unadjusted and Adjusted Conditional Logistic Regression Models for Associations between Co-stimulating Molecules and non-AIDS events at Three Time-points.**

| Biomarker | Baseline (pre-ART)<br>N=163                  |                                  | Year 1 (post-ART)<br>N=323                   |                                  | Pre-Event<br>N=252                           |                                  |
|-----------|--|----------------------------------|--|----------------------------------|--|----------------------------------|
|           | Unadjusted OR (95% CI) per one IQR; p-value* | Range of Adjusted OR per one IQR | Unadjusted OR (95% CI) per one IQR; p-value* | Range of Adjusted OR per one IQR | Unadjusted OR (95% CI) per one IQR; p-value* | Range of Adjusted OR per one IQR |
| CD27      | <b>2.1 (1.2, 3.6); p=0.01</b>                | 1.9 – 2.3                        | <b>1.6 (1.2, 2.2); p=0.001</b>               | 1.6 – 1.7                        | <b>2.1 (1.4, 3.3); p&lt;0.001</b>            | 1.9 – 2.3                        |
| CD28      | 1.3 (0.8, 2.1); p=0.30                       | 1.1 – 1.3                        | 1.0 (0.7, 1.3); p=0.93                       | 0.9 – 1.0                        | 1.4 (0.9, 2.1); p=0.11                       | 1.2-1.4                          |
| CD40      | <b>1.8 (1.1, 2.8); p=0.02</b>                | 1.5 – 1.8                        | 1.2 (0.9, 1.6); p=0.51                       | 1.1 – 1.2                        | <b>1.7 (1.2, 2.5); p=0.01</b>                | 1.4 – 1.7                        |
| GITR      | 1.2 (0.8, 1.9); p=0.33                       | 1.2 – 1.3                        | 0.9 (0.7, 1.2); p=0.51                       | 0.8 – 0.9                        | 1.3 (0.9, 1.7); p=0.15                       | 1.1 – 1.3                        |
| GITRL     | 1.4 (0.9, 2.1); p=0.16                       | 1.3 – 1.4                        | 1.1 (0.8, 1.4); p=0.69                       | 1.0 – 1.1                        | <b>1.6 (1.0, 2.4); p=0.03</b>                | 1.3 – 1.6                        |
| HVEM      | 1.3 (0.9, 2.0); p=0.20                       | 1.0 – 1.3                        | 1.1 (0.9, 1.4); p=0.48                       | 1.0 – 1.1                        | 1.4 (1.0, 1.9); p=0.09                       | 1.2 – 1.4                        |
| BTLA      | 1.3 (0.8, 2.1); p=0.23                       | 1.2 – 1.4                        | 1.0 (0.7, 1.3); p=0.88                       | 0.9 – 1.0                        | 1.4 (0.9, 2.0); p=0.11                       | 1.2 – 1.4                        |
| ICOS      | 1.4 (0.9, 2.2); p=0.16                       | 1.3 – 1.4                        | 1.0 (0.7, 1.3); p=0.85                       | 0.9 – 1.0                        | 1.3 (0.9, 1.9); p=0.13                       | 1.2 – 1.3                        |

\*noteworthy results are bold  
Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio  
Adjustments were done individually for the following covariates: i.) HIV-disease measure (Baseline: log<sub>10</sub> HIV RNA level, Post-Baseline: CD4 cell count); ii.) Time updated chronic Hepatitis B/C status; iii.) Time updated smoking status; iv.) Baseline injection drug use; v.) Time updated waist-to-hip ratio; vi.) Time updated diabetes status; vii.) Time updated hypertension status; viii.) Time updated use of antihypertensive or lipid lowering medications; and ix.) Time updated family history of myocardial infarction

**528 SOLUBLE IMMUNE COSTIMULATORY MOLECULES ARE PREDICTIVE OF NON-AIDS EVENTS**

**Thomas A. Premeaux<sup>1</sup>**, Carlee B. Moser<sup>2</sup>, Ashley McKhann<sup>2</sup>, Stephen Yeung<sup>1</sup>, Alina Pang<sup>1</sup>, Micheal Corley<sup>1</sup>, Alan Landay<sup>3</sup>, Sara Gianella<sup>4</sup>, Lishomwa Ndhlovu<sup>1</sup>  
<sup>1</sup>Weill Cornell Medicine, New York, NY, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Rush University Medical Center, Chicago, IL, USA, <sup>4</sup>University of California San Diego, San Diego, CA, USA

**Background:** Despite suppressive antiretroviral therapy (ART), people with HIV (PWH) experience an increased risk of morbidity and mortality, in part due to chronic inflammation and immune dysfunction. Immune co-stimulatory molecules exist in soluble forms at normal physiological conditions and many are elevated in cancer, HIV infection, and other inflammatory diseases, suggesting they could serve as promising early predictive biomarkers of adverse outcomes in PWH. We aimed to identify relationships between plasma levels of soluble immune co-stimulatory molecules with the incidence of non-AIDS events (NAEs) utilizing a nested case-control study from the AIDS Clinical Trials Group ALLRT cohort.

**Methods:** Study participants were evaluated at baseline (pre-ART; 66 cases, 97 controls), 1 year post-ART (112 cases, 211 controls), and immediately preceding an event (89 cases, 163 controls). NAEs (cases) include myocardial infarction (MI)/stroke, malignancy, serious bacterial infection, and non-accidental death. Matched controls had an event-free follow-up equal or greater than that of the relevant case. All participants were virally suppressed on ART at year 1 and matched for age (within 10 years, median 45 years), sex (84% male), pre-ART CD4+ T cell count (within 50 cells/mm<sup>3</sup>, median 213 cells/mm<sup>3</sup>), ART regimen at 1 year, and parent study. Soluble co-stimulatory molecules CD27, CD28, CD40, GITR, GITRL, HVEM, BTLA, and ICOS were measured by Luminex. Conditional logistic regression analysis assessed associations of co-stimulatory molecules and events, adjusting for pertinent covariates at each timepoint; noteworthy associations used a threshold of an effect size (OR per one IQR) ≥1.5.

**Results:** Higher levels of CD27 were associated with increased risk of NAEs at each time point: baseline [unadjusted odds ratio (OR) per 1 IQR =2.1, p=0.008], year 1 (OR=1.6, p=0.001), pre-event (OR=2.1, p<0.001). Higher levels CD40 was associated with increased risk of NAEs at baseline (OR=1.8, p=0.019) and pre-event (OR=1.7, p=0.008). These associations remained after adjustments for HIV RNA levels and CD4 counts. Furthermore, examining specific NAEs, higher CD27 was associated with both increased risk of death and MI/stroke at multiple time points (OR= 2.9-5.3) and CD40 associated with malignancy at baseline and pre-event (OR=2.3-2.4).

**Conclusion:** Soluble CD27 and CD40 are predictive of NAEs and may inform interventional studies aimed to reduce morbidity and mortality in PWH on suppressive ART.

**529 PLASMA GALECTIN-9 AS A PREDICTOR OF NON-AIDS EVENTS DURING SUPPRESSIVE ART**

**Thomas A. Premeaux<sup>1</sup>**, Carlee B. Moser<sup>2</sup>, Ashley McKhann<sup>2</sup>, Martin Hoenig<sup>3</sup>, Michael M. Lederman<sup>4</sup>, Alan Landay<sup>5</sup>, Sara Gianella<sup>3</sup>, Lishomwa Ndhlovu<sup>1</sup>  
<sup>1</sup>Weill Cornell Medicine, New York, NY, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of California San Diego, San Diego, CA, USA, <sup>4</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>5</sup>Rush University Medical Center, Chicago, IL, USA

**Background:** People with HIV (PWH) on antiretroviral therapy (ART) still experience an increased risk of morbidity and mortality, which is partly driven by chronic inflammation. We previously demonstrated that soluble galectin-9 (Gal-9), a pleiotropic glycan-binding immunomodulatory protein, is elevated in PWH on ART and associated with markers of HIV persistence, neurological complications and indices of morbidity and mortality in HIV infection. Here, we aimed to identify relationships between Gal-9 and the occurrence of non-AIDS events (NAEs) in PWH on suppressive ART, utilizing a nested case-control study from the AIDS Clinical Trials Group ALLRT cohort.

**Methods:** Study participants were evaluated at baseline (pre-ART; 66 cases, 97 controls), 1 year post-ART (112 cases, 211 controls), and immediately preceding an event (89 cases, 162 controls). NAEs (cases) include myocardial infarction/stroke, malignancy, serious bacterial infection, and non-accidental death. Matched controls had an event-free follow-up equal or greater than that of the relevant case. All participants were virally suppressed by ART by year 1 and matched for age (within 10 years, median 45 years), sex (84% male), pre-ART CD4+ T cell count (within 50 cells/mm<sup>3</sup>, median 213 cells/mm<sup>3</sup>), ART regimen at 1 year, and parent study. Gal-9 levels in plasma were assessed by ELISA. Conditional logistic regression analysis assessed associations of Gal-9 with NAEs. Spearman correlations assessed associations between biomarkers among the controls.

**Results:** Higher plasma levels of Gal-9 were associated with increased risk of NAEs at year 1 and pre-event (unadjusted OR per 1 IQR (95% CI) = 1.4 (1.0, 1.9), p=0.04 and OR=1.6 (1.0, 2.3), p=0.03). Association at year 1 remained significant with adjustment for CD4 count. Higher levels of Gal-9 were associated with specific NAEs, MI/stroke (OR= 1.9) and death (OR=2.8) at year 1 and malignancy (OR=1.8) pre-event. Gal-9 also correlated with markers previously assessed to be predictive of NAEs, including sTNFR-1, sTNFR-II, and suPAR, at each timepoint (all r ≥0.45, p<0.0001).

**Conclusion:** Elevated plasma Gal-9 levels are predictive of NAEs; due to the pleiotropic nature of Gal-9 it may be an ideal target for intervention to help attenuate chronic immune activation and, as a result, lessen the risk of morbidity during suppressive ART.

**Table 1:** Spearman Correlations for Gal-9 with Soluble Inflammatory and Immune Activation Markers at Three Time-points Among the Controls.

| Biomarker       | Baseline (i.e. before ART)<br>N=148 | Year 1<br>N=252                     | Pre-Event<br>N=205                  |
|-----------------|-------------------------------------|-------------------------------------|-------------------------------------|
|                 | Correlation with Gal-9;<br>p-value* | Correlation with Gal-9;<br>p-value* | Correlation with Gal-9;<br>p-value* |
| IL-6            | <b>r=0.45</b><br><b>p&lt;0.0001</b> | r=0.28<br>p<0.0001                  | r=0.27<br>p<0.0001                  |
| <b>sTNFR-I</b>  | <b>r=0.60</b><br><b>p&lt;0.0001</b> | <b>r=0.53</b><br><b>p&lt;0.0001</b> | <b>r=0.45</b><br><b>p&lt;0.0001</b> |
| <b>sTNFR-II</b> | <b>r=0.64</b><br><b>p&lt;0.0001</b> | <b>r=0.61</b><br><b>p&lt;0.0001</b> | <b>r=0.52</b><br><b>p&lt;0.0001</b> |
| <b>suPAR</b>    | <b>r=0.53</b><br><b>p&lt;0.0001</b> | <b>r=0.55</b><br><b>p&lt;0.0001</b> | <b>r=0.47</b><br><b>p&lt;0.0001</b> |
| sCD163          | r=0.23<br>p=0.004                   | r=0.35<br>p<0.0001                  | r=0.31<br>p<0.0001                  |
| sCD14           | <b>r=0.59</b><br><b>p&lt;0.0001</b> | r=0.24<br>p<0.0001                  | r=0.29<br>p<0.0001                  |
| IP-10           | <b>r=0.55</b><br><b>p&lt;0.0001</b> | r=0.32<br>p<0.0001                  | r=0.42<br>p<0.0001                  |
| D-dimer         | <b>r=0.50</b><br><b>p&lt;0.0001</b> | r=0.20<br>p=0.001                   | r=0.20<br>p=0.004                   |
| BDG             | r=0.32<br>p<0.0001                  | r=0.00<br>p=0.97                    | r=0.06<br>p=0.36                    |
| LBP             | r=0.36<br>p<0.0001                  | r=0.12<br>p=0.06                    | r=0.21<br>p=0.003                   |
| I-FABP          | r=0.22<br>p=0.008                   | r=0.05<br>p=0.42                    | r=0.05<br>p=0.50                    |

\*noteworthy results are bold

**530 FEMINIZING THERAPY DECREASES D-DIMER BUT WORSENS INSULIN SENSITIVITY IN TRANS WOMEN**

**Jordan Lake<sup>1</sup>**, Hongyu Miao<sup>1</sup>, Aaren Kettelhut<sup>2</sup>, Jesse Clark<sup>3</sup>, Javier R. Lama<sup>4</sup>, Sari Reinsner<sup>5</sup>, Kenneth H. Mayer<sup>6</sup>, Amaya Perez-Brumer<sup>7</sup>, Nicholas Funderburg<sup>8</sup>  
<sup>1</sup>UTHealth, Houston, TX, USA, <sup>2</sup>O&M School of Medicine, Santo Domingo, Dominican Republic, <sup>3</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>4</sup>Asociación Civil Impacta Salud y Educación, Lima, Peru, <sup>5</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>6</sup>Fenway Health, Boston, MA, USA, <sup>7</sup>University of Toronto, Toronto, Canada, <sup>8</sup>Ohio State University, Columbus, OH, USA

**Background:** Feminizing hormonal therapies (FHT) and HIV are known to increase cardiovascular risk for transgender women (TW), though little data exists to quantify cardiometabolic changes following FHT initiation, particularly among TW living with HIV (HIV+).

**Methods:** The Féminas study enrolled 220 TW from October 2016–March 2017 in Lima, Peru. Participants were of HIV negative (HIV-) or unknown serostatus or HIV+ but out of care, and reported recent sexual activity that was high risk (i.e., condomless intercourse, partner discordance) for HIV acquisition and/or transmission. All received HIV/STI testing and access to FHT (estradiol valerate and spironolactone), PrEP (TDF/FTC) or ART (TDF/FTC/EFV) for 12 months. Serum was stored for cardiometabolic biomarker measurement; fasting glucose and lipid parameters were measured in real time.

**Results:** 171 TW (32 HIV+, 139 HIV-) had stored samples for analysis. Median age was 26 years, 70% had history of prior FHT use. At baseline, PCSK9, sCD14, sCD163, IL-6, sTNFR/II, CRP and EN-RAGE levels were significantly (p<0.05) higher in HIV+ vs HIV- TW, whereas HDL and total cholesterol were lower, and insulin and glucose parameters were similar (data not shown). All HIV+ TW started ART, but only 5 achieved HIV RNA <50 copies/mL at any time on study. No HIV- TW initiated PrEP. All participants initiated FHT. Over 6 months, HIV- and HIV+ TW on FHT had worsening insulin, glucose and HOMA-IR values (Table 1). Large decreases in d dimer also occurred. Though potentially clinically significant for individuals, variability was very high, preventing observation of statistical significance for the cohort. Similar changes in HIV- and HIV+ TW suggest that persistent viremia did not obscure FHT effects.

**Conclusion:** In this unique cohort, FHT initiation appeared to decrease d dimer but worsen insulin sensitivity for both HIV+ and HIV- TW. Because PrEP uptake and ART adherence were very low, these effects seem primarily due to FHT use. Further study is needed to better understand cardiometabolic changes in TW by HIV serostatus and to optimize uptake of, and adherence to, HIV prevention and treatment options.

|                  | HIV-                 |                     |                     | HIV+                 |                      |                      |                      |
|------------------|----------------------|---------------------|---------------------|----------------------|----------------------|----------------------|----------------------|
|                  | Month 0              | Month 6             | Month 12            | Month 0              | Month 6              | Month 12             |                      |
| d dimer (ng/mL)  | 171.9 (118.3, 336.2) | 127.9 (83.7, 205.2) | 126.2 (62.4, 187.1) | 271.2 (140.1, 382.4) | 160.2 (115.1, 228.8) | 145.9 (106.1, 273.8) |                      |
| Insulin (pmol/L) | 26.9 (19.3, 42.7)    | 39.2 (28.0, 67.8)   | 36.2 (22.7, 66.3)   | 25.6 (18.4, 43.5)    | 33.8 (24.3, 53.4)    | 34.5 (23.4, 75.9)    |                      |
| Glucose (mg/dL)  | 87.7 (62.4, 92.7)    | 90.6 (66.1, 95.3)   | 89.5 (66.4, 95.0)   | 85.5 (61.7, 90.1)    | 92.7 (68.3, 95.8)    | 89.6 (65.5, 95.5)    |                      |
| HOMA-IR          | 0.8 (0.6, 1.4)       | 1.3 (0.9, 2.2)      | 1.1 (0.8, 2.3)      | 0.8 (0.6, 1.3)       | 1.2 (0.8, 1.7)       | 1.1 (0.8, 2.6)       |                      |
|                  | 6-Month Changes      |                     |                     | 12-Month Changes     |                      |                      |                      |
|                  | HIV-                 | HIV+                | %                   | HIV-                 | HIV+                 | %                    |                      |
| d dimer (ng/mL)  | -33.6 (-158.6, 33.0) | -19                 | -5.5 (-285.8, 36.6) | -2                   | -59.7 (-175.7, 10.6) | -36                  | -51.1 (-251.6, -0.9) |
| Insulin (pmol/L) | 8.9 (-3.2, 31.0)     | +32                 | 5.7 (-8.1, 30.7)    | +22                  | 6.6 (-2.9, 25.7)     | +24                  | 7.0 (-0.5, 46.6)     |
| Glucose (mg/dL)  | 3.6 (-2.9, 9.5)      | +4                  | 5.0 (2.2, 12.5)     | +6                   | 2.9 (-3.0, 9.1)      | +3                   | 2.8 (-1.9, 10.0)     |
| HOMA-IR          | 0.3 (-0.1, 1.1)      | +33                 | 0.2 (-0.3, 1.1)     | +25                  | 0.2 (-0.2, 1.2)      | +27                  | 0.3 (-0.1, 1.4)      |
| P value          | 0.37 - 0.48          |                     | 0.41 - 0.46         | 0.35 - 0.48          |                      | 0.46 - 0.53          |                      |

**531 LOWER PLASMA PHOSPHOCHOLINE ABUNDANCE IS ASSOCIATED WITH NAFLD IN PWH**

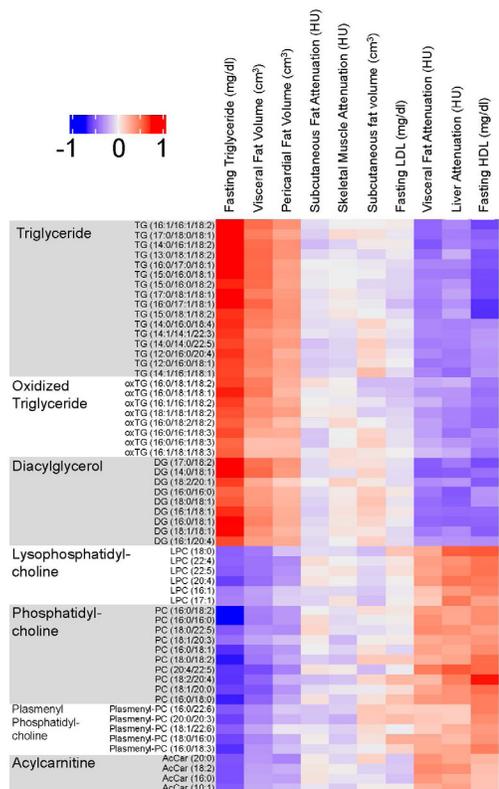
**Curtis L. Gabriel<sup>1</sup>**, Fei Ye<sup>1</sup>, Run Fan<sup>1</sup>, Celestine Wanjalla<sup>1</sup>, Mona Mashayekhi<sup>1</sup>, Samuel Bailin<sup>1</sup>, Jane Ferguson<sup>1</sup>, John Koethe<sup>1</sup>  
<sup>1</sup>Vanderbilt University, Nashville, TN, USA

**Background:** Over 1.1 million people in the United States are living with human immunodeficiency virus (HIV), and liver disease is the leading cause of non-AIDS-related mortality in persons with HIV (PWH). PWH suffer a disproportionate burden of non-alcoholic fatty liver disease (NAFLD) compared to HIV-negative persons which confers higher rates of morbidity and mortality through the complications of cirrhosis, cardiovascular disease and diabetes. Identification of metabolites associated with the accumulation of liver fat may identify novel screening biomarkers and therapeutic targets. However, there are few data describing the metabolic pathways that predispose PWH to NAFLD.

**Methods:** 109 PWH on long-term viral suppression were recruited for this study. Non-contrasted chest and abdominal CT scans assessed liver, abdominal subcutaneous (SAT) and visceral adipose tissue (VAT), and skeletal muscle attenuation (a measure of lipid content) and pericardial fat, SAT, and VAT volumes. Plasma was collected after an overnight fast and relative abundance of plasma lipid species was measured using untargeted liquid chromatography-mass spectrometry. Lipid species abundances were related to the CT tissue characteristics using linear regression modeling.

**Results:** 22% of participants were female and the mean age was 46 years old. 53% were Caucasian and the mean BMI was 33.3 kg/m<sup>2</sup>. Participants had been on antiretroviral therapy for an average of 9 years and total CD4+ T cell count among subjects averaged 498 cells/mm<sup>3</sup>. Lower levels of phosphocholines, including lysophosphatidylcholine and phosphatidylcholine, was associated with lower hepatic attenuation (indicative of steatosis; see figure). Higher abundance of triglycerides was associated with higher levels of hepatic steatosis. The lipidome profile observed in participants with greater hepatic steatosis was similar to the profiles in participants with higher VAT and pericardial fat volume. Of note, this lipid profile was not observed in SAT or skeletal muscle density.

**Conclusion:** PWH with hepatic steatosis and higher visceral adiposity had lower abundances of plasma phosphocholines and increased abundances of triglyceride species. Intestinal dysbiosis has previously been shown to be related to impairment of phosphocholine metabolism. Future studies will determine whether changes in the intestinal microbiome contribute to a pathogenic plasma lipidome in PWH with NAFLD and ectopic fat deposition in other tissues.



**532 INDEPENDENT ASSOCIATIONS OF TNF-ALPHA AND IL-1 BETA WITH EMPHYSEMA IN HIV INFECTION**

**Rebeka F. Thudium<sup>1</sup>**, Hedda Ringheim<sup>1</sup>, Andreas Ronit<sup>2</sup>, Thomas Benfield<sup>2</sup>, Amanda Mccroft<sup>3</sup>, Jan Gerstoft<sup>1</sup>, Marius Trøseid<sup>4</sup>, Alvaro H. Borges<sup>5</sup>, Sisse R. Ostrowski<sup>1</sup>, Jørgen Vestbo<sup>6</sup>, Susanne D. Nielsen<sup>1</sup>

<sup>1</sup>Rigshospitalet, Copenhagen, Denmark, <sup>2</sup>Hvidovre Hospital, Hvidovre, Denmark, <sup>3</sup>Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), University College London, London, UK, <sup>4</sup>Oslo University Hospital, Oslo, Norway, <sup>5</sup>Statens Serum Institut, Copenhagen, Denmark, <sup>6</sup>University of Manchester, Manchester, UK

**Background:** Emphysema has been suggested to occur more frequently and at younger age in people living with HIV (PLWH) than in uninfected controls. Risk factors for emphysema include smoking and alpha-1 antitrypsin (AAT) deficiency, but recent evidence suggest that inflammation may also play a role. We investigated whether elevated cytokine concentrations (interleukin(IL)-1 $\beta$ , IL-1 receptor antagonist (IL-1RA), IL-2, IL-4, IL-6, IL-10, IL-17A, tumor necrosis factor-alpha (TNF $\alpha$ ), interferon-gamma (IFN $\gamma$ ), soluble CD14 (sCD14) and sCD163) are independently associated with radiographic emphysema in PLWH. **Methods:** We included PLWH without hepatitis B and C co-infection with a plasma sample and a chest computed tomography scan available from the Copenhagen Comorbidity in HIV Infection (COCOMO) Study. Radiographic emphysema plus trace emphysema was defined as percentage of low attenuation area under 950 Hounsfield units (%LAA-950) using a cut-off at 5%. Cytokine concentrations were measured by ELISA or Luminex immunoassays, and an elevated cytokine concentration was defined as above the 75th percentile. Logistic regression analyses were performed to explore associations between elevated cytokine concentrations and radiographic emphysema plus trace emphysema in PLWH.

**Results:** Of 783 PLWH, 147 (18.8%) had emphysema plus trace emphysema. PLWH were predominantly male (86.0%) and 743 (94.9%) had undetectable viral load. PLWH with emphysema plus trace emphysema had higher concentrations of TNF $\alpha$  (median (IQR): 8.2 (6.4-9.8) versus 7.1 (5.7-8.6) pg/ml, p<0.001), IL-1 $\beta$  (median (IQR): 0.21 (0.1-0.4) versus 0.17 (0.1-0.3) pg/ml, p=0.004) and IL-6 (median (IQR): 3.6 (2.6-4.9) versus 3.1 (2.0-4.3) pg/ml, p=0.023) than PLWH without. AAT deficiency (<1.0 g/L) was rare and equally prevalent in the two groups (p=0.291). In models adjusted for age, sex, ethnicity, smoking status, BMI and CD4 nadir, elevated TNF $\alpha$  (adjusted odds ratio (aOR): 1.91 [95%CI: 1.23-2.95], p=0.004) and IL-1 $\beta$  (aOR: 1.93 [95%CI: 1.25-3.00], p=0.003) were associated with emphysema plus trace emphysema (Table 1). The association between IL-1 $\beta$  and emphysema was modified by smoking (p-interaction=0.018) with a more pronounced association in never smokers (aOR: 4.87 [95%CI: 2.22-10.69], p<0.001).

**Conclusion:** Two markers of systemic inflammation, TNF $\alpha$  and IL-1 $\beta$ , were independently associated with radiographic emphysema plus trace emphysema in PLWH and may be involved in the pathogenesis of emphysema.

**Table 1: Multivariable logistic regression analyses for the association between elevated cytokine concentration (above the 75<sup>th</sup> percentile) and emphysema plus trace emphysema in PLWH.**

|              | Model 1 <sup>a</sup><br>Risk of emphysema plus trace emphysema<br>High cytokine level vs low<br>aOR [95% CI] | p-value | Model 2 <sup>b</sup><br>Risk of emphysema plus trace emphysema<br>High cytokine level vs low<br>aOR [95% CI] | p-value |
|--------------|--|---------|--|---------|
| TNF $\alpha$ | 1.89 [1.26-2.83]   | 0.002   | 1.91 [1.23-2.95]   | 0.004   |
| IL-1 $\beta$ | 1.72 [1.14-2.59]   | 0.009   | 1.93 [1.25-3.00]   | 0.003   |
| IL-1RA       | 1.15 [0.75-1.76]   | 0.534   | 1.32 [0.83-2.11]   | 0.238   |
| IL-2         | 1.19 [0.78-1.81]   | 0.417   | 1.36 [0.87-2.13]   | 0.175   |
| IL-4         | 1.07 [0.67-1.70]   | 0.782   | 1.28 [0.79-2.09]   | 0.316   |
| IL-6         | 1.07 [0.70-1.66]   | 0.746   | 1.39 [0.87-2.23]   | 0.167   |
| IL-10        | 1.15 [0.75-1.75]   | 0.530   | 1.23 [0.78-1.92]   | 0.372   |
| IL-17A       | 1.27 [0.84-1.92]   | 0.262   | 1.23 [0.79-1.92]   | 0.352   |
| IFN $\gamma$ | 1.09 [0.71-1.67]   | 0.697   | 1.12 [0.71-1.76]   | 0.617   |
| sCD14        | 0.87 [0.56-1.36]   | 0.549   | 0.93 [0.58-1.48]   | 0.752   |
| sCD163       | 1.02 [0.66-1.58]   | 0.926   | 1.24 [0.78-1.98]   | 0.366   |
| AAT          | 0.75 [0.47-1.19]   | 0.224   | 0.78 [0.47-1.30]   | 0.345   |

<sup>a</sup> Model 1 adjusted for age and sex. <sup>b</sup> Model 2 adjusted for age, sex, ethnicity, smoking status, BMI and CD4 nadir. Each cytokine was added to model 1 and 2, one at a time. Emphysema plus trace emphysema was defined as percentage of low attenuation area under 950 Hounsfield units (%LAA-950) > 5%. Abbreviations: PLWH, people living with HIV; TNF $\alpha$ , Tumor necrosis factor-alpha; IL-1 $\beta$ , interleukin-1 beta; IL-1RA, interleukin-1 receptor antagonist; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; IL-17A, interleukin-17A; IFN $\gamma$ , interferon-gamma; sCD14, soluble CD14; sCD163, soluble CD163; AAT, alpha-1 antitrypsin.

**533 ASSOCIATION OF NADIR CD4/CD8 WITH CVD AND NON-AIDS-DEFINING CANCERS IN THE DC COHORT**

**Letumile R. Moeng<sup>1</sup>**, Morgan Byrne<sup>2</sup>, Anne Monroe<sup>2</sup>, Vishnu Priya Mallipeddi<sup>1</sup>, Michael A. Horberg<sup>3</sup>, Amanda Castel<sup>2</sup>, Ronald Wilcox<sup>1</sup>, for the DC Cohort Executive Committee

<sup>1</sup>Howard University, Washington, DC, USA, <sup>2</sup>George Washington University, Washington, DC, USA, <sup>3</sup>Kaiser Permanente Mid-Atlantic States, Rockville, MD, USA

**Background:** HIV has transitioned from a progressive, fatal disease to a chronic, manageable disease marked by elevated risk of cardiovascular diseases (CVD). Rates of myocardial infarction, heart failure, stroke and other CVD manifestations are significantly higher for people with HIV (PWH), even with antiretroviral therapy (ART). The era of ART has also seen an increase in the burden of non-AIDS defining cancers (NADC). Low CD4/CD8 has been associated with increased risk of CVD and NADC amongst PWH in previous studies. Data on clinical use of nadir CD4/CD8 is limited. To address this knowledge gap, we investigated the association between nadir CD4/CD8 and CVD and NADC.

**Methods:** Data from PWH aged >18 years enrolled Jan 2011-Mar 2019 in the DC Cohort, a longitudinal study using data from electronic health records of PWH in care at 15 clinics in Washington, DC, were analyzed. Eligible participants had at least 3 CD4/CD8, each separated by at least 90 days, during follow-up. The relationship between nadir CD4/CD8 and demographic and clinical characteristics was examined using  $\chi^2$  test. Multivariable logistic models were used to evaluate the association of nadir CD4/CD8 with new CVD and NADC (analyzed separately) occurring at any time during follow up, adjusting for age, gender, race and smoking status. Diabetes, insurance status, LDL and HDL were also used to adjust for CVD outcomes.

**Results:** 3,868 participants were included. Median follow up was 5.1 years. At CD4/CD8 nadir, 732 (19%) were <35y, 1404 (36%) 35-50y, 1512 (39%) 51-65, and 220 (6%)  $\geq$ 65y; 70% male; 70% Non-Hispanic (NH) Black, 14% NH White, and 5% Hispanic; 63.9% publicly insured, 2.5% diabetic 43% were current smokers. 24.6% low (<40 mg/dL) HDL. Increased age, lower nadir CD4/CD8 (CD4/CD8: 0.5  $\leq$  x <1.0 = adjusted odds ratio (aOR) 1.53; CD4/CD8: < 0.5 = aOR 1.94), public health insurance, diabetes and lower HDL were all associated with increased odds of CVD (p<.05 for all). For non-AIDS cancers, female gender was associated with decreased odds, while Hispanic ethnicity (aOR 2.57, p < 0.006) and nadir CD4/CD8 ratio <0.5 (aOR 2.14; p < 0.034) were associated with increased odds.

**Conclusion:** In a large urban cohort of PLWH, a nadir CD4/CD8 <0.5 was associated with CVD and NADC. Low nadir CD4/CD8 likely portends increased risk and could be a useful screening measure for CVDs and NADC among PWH.

**Table 1. Multivariable Logistic Regression for Cardiovascular and Non-AIDS associated Cancer controlling for Demographic, clinical, and predictors of disease.**

| Characteristics       | CVD <sup>a</sup><br>N=430 |         | NADC <sup>b</sup><br>N=104 |         |
|-----------------------|---------------------------|---------|----------------------------|---------|
|                       | aOR 95%CI                 | P-value | aOR 95%CI                  | P-value |
| Age at CD4/8 nadir, y | 1.06 (1.04-1.07)          | <.0001  | 1.01 (1.00-1.03)           | 0.1194  |
| Gender                |                           |         |                            |         |
| Male                  | Ref                       |         | Ref                        |         |
| Female                | 1.27 (0.99-1.62)          | 0.0578  | 0.48 (0.27-0.86)           | 0.0136  |
| Transgender           | 0.90 (0.44-1.85)          | 0.7810  | 0.81 (0.27-2.62)           | 0.7208  |
| Race/Ethnicity        |                           |         |                            |         |
| Non-Hispanic Black    | Ref                       |         | Ref                        |         |
| Non-Hispanic White    | 1.06 (0.76-1.48)          | 0.7378  | 1.34 (0.78-2.29)           | 0.2877  |
| Hispanic              | 0.78 (0.40-1.54)          | 0.4763  | 2.57 (1.30-5.07)           | 0.0066  |
| Other/ Unknown        | 1.03 (0.58-1.83)          | 0.9156  | 1.32 (0.52-3.34)           | 0.5570  |
| Smoking Status        |                           |         |                            |         |
| Never                 | Ref                       |         | Ref                        |         |
| Current               | 1.22 (0.96-1.55)          | 0.1072  | 0.83 (0.54-1.28)           | 0.4000  |
| Previously            | 1.22 (0.87-1.72)          | 0.2385  | 0.73 (0.38-1.43)           | 0.3602  |
| CD4/CD8 nadir ratio   |                           |         |                            |         |
| 1.0 $\leq$            | Ref                       |         | Ref                        |         |
| 0.5 $\leq$ x <1.0     | 1.53 (1.02-2.32)          | 0.0423  | 0.79 (0.36-1.75)           | 0.5590  |
| < 0.5                 | 1.94 (1.31-2.87)          | 0.0010  | 2.14 (1.06-4.32)           | 0.0346  |
| Health Insurance      |                           |         |                            |         |
| Private               | Ref                       |         |                            |         |
| Public                | 1.88 (1.39-2.55)          | <.0001  |                            |         |
| Other/Unknown/None    | 1.31 (0.79-2.17)          | 0.2900  |                            |         |
| Diabetes M.           |                           |         |                            |         |
| No                    | Ref                       |         |                            |         |
| Yes                   | 2.96 (1.86-4.71)          | <.0001  |                            |         |
| HDL, (<40 vs 40+)     | 1.33 (0.4-1.70)           | 0.0214  |                            |         |
| LDL, <130 vs 130+     | 1.07 (0.80-1.43)          | 0.6473  |                            |         |

<sup>a</sup>3355 Participants included in multivariable logistic regression model

<sup>b</sup>3868 Participants included in multivariable logistic regression model

### 534 EPIGENETIC AGING CHANGES IN A COHORT OF AVIREMIC HIV-INFECTED ADULTS

Andrés Esteban-Cantos<sup>1</sup>, Javier Rodriguez-Centeno<sup>1</sup>, Gabriel Saiz-Medrano<sup>2</sup>, Rocío Montejano<sup>1</sup>, Rosa De Miguel<sup>2</sup>, Pilar Barruz<sup>2</sup>, Julián Nevado<sup>2</sup>, Beatriz Mena-Garay<sup>1</sup>, Jose I. Bernardino<sup>1</sup>, Julen Cadiñanos<sup>2</sup>, Eulalia Valencia<sup>1</sup>, Rafael Mican<sup>1</sup>, Mario Mayoral-Muñoz<sup>2</sup>, Jose R. Arribas<sup>1</sup>, Berta Rodes<sup>1</sup>

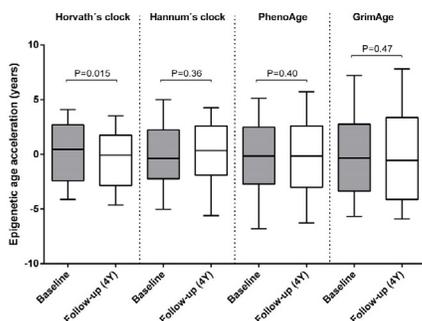
<sup>1</sup>Hospital La Paz Institute for Health Research, Madrid, Spain, <sup>2</sup>La Paz University Hospital, Madrid, Spain

**Background:** Untreated HIV infection causes accentuated epigenetic aging which is partially reversed by antiretroviral therapy (ART) initiation (Lancet HIV, in press). It remains unclear whether epigenetic aging continues to accelerate over time in people living with HIV (PLWH) receiving suppressive ART.

**Methods:** We analyzed 63 participants from a prospective cohort of long-term treated aviremic HIV-infected adults at two timepoints (baseline and 4 years of follow-up). Whole blood DNA methylation profiles were obtained by Illumina Infinium MethylationEPIC BeadChip. We evaluated 4 epigenetic clocks (Horvath and Hannum's clocks, PhenoAge and GrimAge), and calculated epigenetic age acceleration (EAA) for each one as the residuals resulting from the regression of epigenetic age on chronological age using a mixed-effects linear regression model.

**Results:** At baseline, participants were predominantly male (82.5%) and Caucasian (93.7%), median chronological age was 48.7 years (IQR 44.2-53.5), median time since HIV infection diagnosis was 18 years (IQR 13.7-22.3) and median CD4 cell counts was 770 cells/ $\mu$ l (IQR 575-922). 32 participants (50.8%) were receiving a tenofovir (TFV) containing regimen and 31 (49.2%) were never exposed to TFV (of whom 15 were receiving abacavir and 16 a nucleos(t)ide reverse transcriptase inhibitor sparing regimen). All participants were virologically suppressed at the two timepoints. After 4 years of follow up, Horvath-EAA slightly decreased (mean difference: -0.66 years,  $p=0.015$ ), whereas Hannum-EAA, PhenoAge-EAA and GrimAge-EAA did not vary over time (mean differences: 0.05 years,  $p=0.36$ ; 0.39 years,  $p=0.40$  and -0.21 years,  $p=0.47$ ; respectively) (Figure). We found no differences in any EAA measure over time between participants receiving a TFV based-regimen or those never exposed to TFV. Changes in CD4 counts after follow-up were not associated with changes in any of the analyzed EAA measures.

**Conclusion:** Epigenetic aging did not accelerate in a cohort of aviremic HIV-infected adults after four years of follow-up, independently of the antiretroviral regimen and CD4 changes. These results are not consistent with an accelerated biological aging process during successfully treated HIV infection.



### 535 EFFECT OF TENOFOVIR ON TELOMERASE, TELOMERE LENGTH, AND T-CELLS IN AVIREMIC HIV ADULTS

Javier Rodriguez-Centeno<sup>1</sup>, Andrés Esteban-Cantos<sup>1</sup>, Rocío Montejano<sup>1</sup>, Natalia Stella-Ascariz<sup>2</sup>, Beatriz Mena-Garay<sup>1</sup>, Maria Jimenez-Gonzalez<sup>2</sup>, Rosa De Miguel<sup>1</sup>, Berta Rodes<sup>1</sup>, Belen Alejos<sup>2</sup>, Gabriel Saiz-Medrano<sup>1</sup>, Jose I. Bernardino<sup>1</sup>, Julen Cadiñanos<sup>1</sup>, Juan M. Castro-Álvarez<sup>2</sup>, Jose R. Arribas<sup>1</sup>

<sup>1</sup>La Paz University Hospital, Madrid, Spain, <sup>2</sup>Institute of Health Carlos III, Madrid, Spain

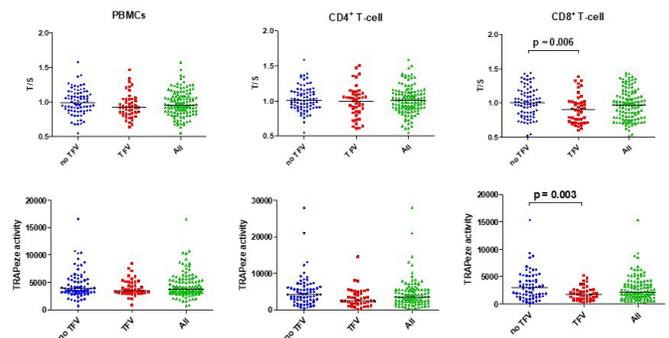
**Background:** Tenofovir (TFV), at therapeutic concentrations, inhibits telomerase activity (TA) in vitro in activated PBMCs from healthy volunteers (J Acquir Immune Defic Syndr 2017; 74:91) and compared to non-TFV-containing regimens, TFV-containing treatments produced smaller gains in whole blood telomere length (TL) after 2 years of follow-up in PLWH with prolonged virological suppression (J Infect Dis 2018; 218:1531). We now report ex vivo,

effects of TFV on TL and TA, in PBMCs, CD4+ and CD8+ T-cells and on T-cell subsets distribution in long-term aviremic HIV+ persons.

**Methods:** We analyzed HIV participants with suppressed virological replication who have been continuously receiving TFV for at least 4 years (TDF,  $n=23$  or TAF,  $n=27$ ) or never exposed to TFV: Abacavir ( $n=60$ ) and N(t)RTI-sparing regimens ( $n=21$ ). PBMCs were isolated using density gradient media. CD4+ and CD8+ T-cells were isolated from fresh PBMCs by magnetic separation. We measured TL (T/S ratio) with monochrome multiplex qPCR and TA using the TRAPeze RT Telomerase Detection Kit. CD4+ and CD8+ T-cell subsets were analysed by flow cytometry from fresh PBMCs: Recent Thymic Emigrants (RTE) (CD31+CD45RA+CD27+), naive (CD45RA+CD27+), central Memory (CD45RA-CD27+), effector memory (CD45RA-CD27-), TEMRA (CD45RA+CD27-), senescent (CD28-CD57+), exhausted (PD1+) and activated (CD38+HLADR+).

**Results:** 131 participants. Male (%): 77.1, age (y): 53.4 (IQR 49.3-57.5), Caucasian (%): 92.4, duration of known HIV infection (y): 21.1 (IQR 16.4-25.5), CD4 and CD8 T (cells/ $\mu$ l): 725 (IQR 520-934) and 610 (IQR 435-785). Adjusting for sex, age, ethnicity, duration of known HIV infection and total CD8+ T-cells the TFV group had significantly shorter TL ( $0.91 \pm 0.21$ ) and diminished TA ( $1952.17 \pm 1258.51$ ) in CD8+ T-cells than the non-TFV group (TL:  $1.01 \pm 0.21$ ; TA:  $3358.14 \pm 2622.92$ ) but not in PBMC or CD4+ T-cells (Figure). No differences were observed in T-cell subsets distribution between groups.

**Conclusion:** In long-term aviremic PLWH, TFV treatment was associated with shorter telomeres in CD8+ T-cells, possibly due to the inhibition of telomerase activity. Treatment with TFV was not associated with changes in T cell subpopulations distribution.



### 536 SERUM LEVEL OF CELL-FREE DNA FRAGMENTS IS ASSOCIATED WITH FRAILITY AND SEVERITY OF HIV

Jing Sun<sup>1</sup>, Lolita S. Nidadavolu<sup>2</sup>, Jacquie Astemborski<sup>1</sup>, Damani A. Piggott<sup>3</sup>, Thomas Laskow<sup>2</sup>, Shruti H. Mehta<sup>1</sup>, Todd Brown<sup>2</sup>, Gregory D. Kirk<sup>1</sup>, Peter Abadir<sup>2</sup>, for the AIDS Linked to the IntraVenous Experience (ALIVE)

<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>The Johns Hopkins Hospital, Baltimore, MD, USA

**Background:** After cellular death, circulating cell-free mitochondrial (ccf-mtDNA) and genomic (ccf-gDNA) DNA fragments are released into circulation. The levels of ccf-gDNA fragments can reflect cell turnover, and ccf-mtDNA fragments can be used to distinguish the mode of cell death (apoptotic vs. necrotic) based on their size (short vs. long fragments, respectively). The utility of serum ccf-DNA as a biomarker and indication of aging among people with HIV (PWH) is unclear.

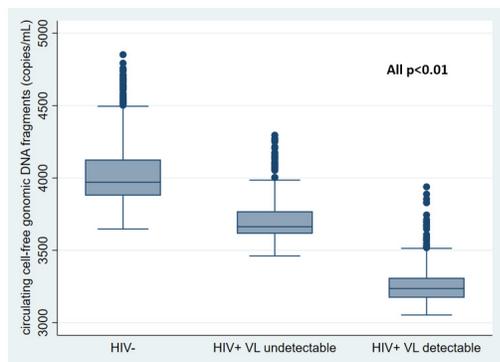
**Methods:** Using ultrasensitive digital PCR, ccf-gDNA and ccf-mtDNA were quantified in serum among HIV-infected and uninfected participants in the AIDS Linked to the IntraVenous Experience (ALIVE) cohort of current and former persons who inject drugs (PWID). Fried frailty phenotype was measured at semi-annual study visits. Linear regression models with generalized estimating equations (GEE) were used to compare differences in log-transformed circulating cell-free DNA fragments by HIV markers after adjusting for covariates (demographics, BMI, drug/alcohol abuse, and white blood cell count). The relationship of ccf-DNA to frailty was assessed using multinomial logistic regression with GEE.

**Results:** Of 1,007 participants followed for 2,810 (median: 3.5) person-years, the median age was 48 years, 46% HIV+ (50% of them virally suppressed), 64% male, 88% black, 52% overweight or obese, 6% had severe drug abuse, and 33% hazardous alcohol drinking at index visit. Compared to people without

HIV, PWH with undetectable (<400 copies/mL) and detectable viral load had lower levels of ccf-gDNA (Figure, predicted mean: 4,025 vs. 3,703 and 3,263 copies/mL, respectively,  $p<0.01$ ) and short (apoptotic) ccf-mtDNA fragments (predicted mean: 7,089 vs. 6,566 and 5,731 copies/mL, respectively,  $p<0.01$ ) after controlling for covariates (all  $p<0.01$ ). Lower levels of ccf-gDNA were significantly associated with frailty (adjusted odds ratio: 1.7, 95% CI: 1.2-2.7), independent of HIV infection, levels of inflammation (IL-6, sTNF-r1, sTNF-r2), and other demographics and behavioral covariates. Over time, ccf-gDNA and short ccf-mtDNA fragments increased significantly in all participants, while levels of long (necrotic) ccf-mtDNA fragments increased only among PWH.

**Conclusion:** Our data suggests circulating cell-free DNA fragments are a promising biomarker to study changes in the rates of cell turnover and as a predictor of higher risk status (frailty) in patients aging with HIV.

Figure. Serum levels of circulating cell-free genomic DNA (ccf-gDNA) fragments by HIV status and viral load in ALIVE cohort (N=1,007).



VL: viral load; VL undetectable: HIV-1 RNA<400 copies/mL; VL detectable: HIV-1 RNA>400 copies/mL.  
 \*Serum levels of circulating cell-free genomic DNA fragments controlled for age, sex, race (black vs. non-black), educational level (high school or more vs. less than high school, BMI (normal vs. overweight vs. obese), drug abuse (Drug Screening Questionnaire identified no abuse vs. low to substantial abuse vs. severe abuse), and alcohol consumption (none vs. moderate vs. hazardous drinking).

We compared, among frailty categories, continuous variables with Kruskal-Wallis tests and categorical variables using Chi-2 tests.

**Results:** 510 PLHIV were included. Subjects had a median age of 73 years [IQR:71-77], 31.3% were >75 years; 81.4% were male (of which 58.1% MSM), 80% were born in France, 27.4% had a history of AIDS, 40.3% had a college education level, and 62.6% were homeowners. At baseline, median HIV duration was 22.7 years, and PLHIV had a median of 3 comorbidities [IQR:2-4]; median CD4 cell count was 562/ L [418-752] and plasma HIV-RNA< 50 copies/mL in 95.3%. Depression and cognitive impairment were present in 24.7% and 59.4%, respectively. 13.5% of the subjects were frail, 63.2% pre-frail, and 23.4% robust. Spontaneous weight loss was observed in 9.7%, low handgrip strength in 56.5%, exhaustion in 31.8%, slow walking speed in 21.5% and low physical activity in 14.8%. Older age, increased comorbidities, lower education level and socioeconomic status were associated with frailty (Table). Lower cognitive performance was more prevalent in pre-frail and frail subjects. Conversely, HIV-related parameters were not associated with frailty.

**Conclusion:** Prevalence of frailty was low in PLHIV aged 70 or older, though nearly two thirds were prefrail. Socio-economic conditions, comorbidities and cognitive function more than HIV-related factors were the main contributors of frailty, suggesting the need of targeted interventions in aging PLHIV with controlled HIV disease.

Table. Participant's characteristics according to Fried frailty phenotype.

| Variables n (%) or median [IQR]  | Total (n=510)    | Robust (n=111, 23.4%) | Pre-frail (n=300, 63.2%) | Frail (n=64, 13.5%) | P-value |
|----------------------------------|------------------|-----------------------|--------------------------|---------------------|---------|
| Age, years                       | 73 [71-77]       | 72 [71-74]            | 73 [71-77]               | 76 [73-81]          | <0.001  |
| Male                             | 415 (81.4)       | 88 (79.3)             | 247 (82.3)               | 47 (73.4)           | 0.85    |
| College education level          | 209 (40.3)       | 54 (48.6)             | 109 (36.3)               | 23 (35.9)           | 0.02    |
| Homeowner                        | 314 (62.6)       | 78 (70.3)             | 180 (60.0)               | 29 (45.3)           | 0.03    |
| CD4/μL at baseline               | 562 [418-752]    | 623 [448-788]         | 565 [423-758]            | 498 [368-661]       | 0.05    |
| Nadir CD4/μL                     | 180 [70-300]     | 185 [84-260]          | 187 [79-308]             | 155 [50-243]        | 0.53    |
| HIV-RNA<50c/mL at baseline       | 487 (95.3)       | 107 (96.4)            | 283 (94.3)               | 55 (85.9)           | 0.42    |
| Duration of HIV infection, years | 22.7 [15.6-28.1] | 22.5 [16.1-27.7]      | 22.8 [15.6-27.7]         | 23.3 [14.7-30.2]    | 0.84    |
| Number of comorbidities          | 3 [2-4]          | 2 [1-3]               | 3 [1-4]                  | 3 [2-5]             | 0.04    |
| Deprived socioeconomic status    | 168 (35.7)       | 23 (20.7)             | 98 (32.7)                | 31 (48.4)           | <0.001  |
| Cognitive impairment             | 298 (59.4)       | 49 (44.1)             | 190 (63.3)               | 39 (60.9)           | <0.001  |

537 PREVALENCE AND DETERMINANTS OF FRAILITY IN PLHIV AGED 70+: ANRS SEPTAVIH STUDY

Clotilde Allavena<sup>1</sup>, Hubert Blain<sup>2</sup>, Xian Abulizi<sup>3</sup>, Mariem Raho Moussa<sup>3</sup>, Laurence Slama<sup>4</sup>, Farouq Boufassa<sup>3</sup>, Christine Katlama<sup>5</sup>, François Raffi<sup>1</sup>, Carole Cagnot<sup>6</sup>, Pierre Delobel<sup>7</sup>, Charles Cazanave<sup>8</sup>, Fabrice Bonnet<sup>9</sup>, Pascal Pugliese<sup>10</sup>, Alain Makinson<sup>11</sup>, Laurence Meyer<sup>12</sup>

<sup>1</sup>Department of Infectious Diseases, University Hospital of Nantes, Nantes, France, <sup>2</sup>Department of Internal Medicine and Geriatrics, University Hospital of Montpellier, Montpellier, France, <sup>3</sup>INSERM U1018, Centre de Recherche en Epidémiologie et Santé des Populations, Le Kremlin-Bicêtre, France, <sup>4</sup>Assistance Publique-Hôpitaux de Paris, Department of Infectious Diseases Hotel Dieu Hospital, Paris, France, <sup>5</sup>Assistance Publique- Hôpitaux de Paris, Department of Infectious Diseases Pitié-Salpêtrière Hospital, Paris, France, <sup>6</sup>National Agency for Research on AIDS and Viral Hepatitis, Paris, France, <sup>7</sup>Department of Infectious Diseases, University Hospital of Toulouse, Toulouse, France, <sup>8</sup>Department of Infectious Diseases, Hôpital Pellegrin, University Hospital of Bordeaux, Bordeaux, France, <sup>9</sup>Department of Infectious Diseases, Hôpital Saint André University Hospital of Bordeaux, Bordeaux, France, <sup>10</sup>Department of Infectious Diseases, University Hospital of Nice, Nice, France, <sup>11</sup>Department of Infectious Diseases, University Hospital of Montpellier, Montpellier, France, <sup>12</sup>INSERM U1018, Centre de Recherche en Epidémiologie et Santé des Populations, University Paris Saclay, Le Kremlin-Bicêtre, France

**Background:** Frailty, a geriatric phenotype at risk of adverse health conditions, has been evaluated in middle-aged people living with HIV (PLHIV). The ANRS EP66 SEPTAVIH multicenter prospective study aims to assess frailty in older PLHIV on antiretroviral treatment.

**Methods:** In 2019, SEPTAVIH enrolled PLHIV aged 70 years or older on antiretroviral treatment for > 12 months from 16 centers in France. Sociodemographic, clinical data and medical/HIV history were collected at baseline. A comprehensive geriatric interview and examination assessed the history and risks of falls, associated medication, physical and cognitive function (MoCA), and mood disorders (CES-D). Frailty was assessed using the 5 criteria Fried frailty phenotype (FFP): recent spontaneous weight loss, low handgrip strength, exhaustion, slow walking speed, and low physical activity. PLHIV were categorized as robust (no criteria), prefrail (1 or 2 criteria) and frail (> 2 criteria).

538 CARDIOVASCULAR RISK SCORE ASSOCIATIONS WITH FRAILITY IN WIHS AND MACS

Mark H. Kuniholm<sup>1</sup>, Elizabeth Vásquez<sup>2</sup>, Allison Appleton<sup>1</sup>, Frank Paella<sup>2</sup>, Matthew Budoff<sup>3</sup>, Erin D. Michos<sup>4</sup>, Deborah Jones Weiss<sup>5</sup>, Adaora Adimora<sup>6</sup>, Igbo Ofotokun<sup>7</sup>, Gypsyamber D'Souza<sup>4</sup>, Kathleen Weber<sup>8</sup>, Phyllis Tien<sup>9</sup>, Michael Plankey<sup>10</sup>, Anjali Sharma<sup>11</sup>, Deborah Gustafson<sup>12</sup>

<sup>1</sup>University at Albany, Albany, NY, USA, <sup>2</sup>Northwestern University, Chicago, IL, USA, <sup>3</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>4</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>5</sup>University of Miami, Miami, FL, USA, <sup>6</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>7</sup>Emory University, Atlanta, GA, USA, <sup>8</sup>Cook County Health and Hospitals System, Chicago, IL, USA, <sup>9</sup>University of California San Francisco, San Francisco, CA, USA, <sup>10</sup>Georgetown University, Washington, DC, USA, <sup>11</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>12</sup>State University of New York Downstate Medical Center, Brooklyn, NY, USA

**Background:** The relationship between cardiovascular disease (CVD) and frailty among people living with HIV is not well established. We hypothesized that 10-year coronary heart disease and atherosclerotic CVD risk computed by Framingham risk score (FRS - 2001 National Cholesterol Education Program Adult Treatment Program III) and Pooled Cohort Equations (PCE - 2013 American College of Cardiology/American Heart Association guidelines) would correlate with the Fried Frailty Phenotype (FFP) in the Women's Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS). The primary objectives were to: 1) estimate associations of FRS and PCE risk with frailty in women and men over 3 time windows and 2) determine whether FRS and/or PCE risk predict incident frailty in men.

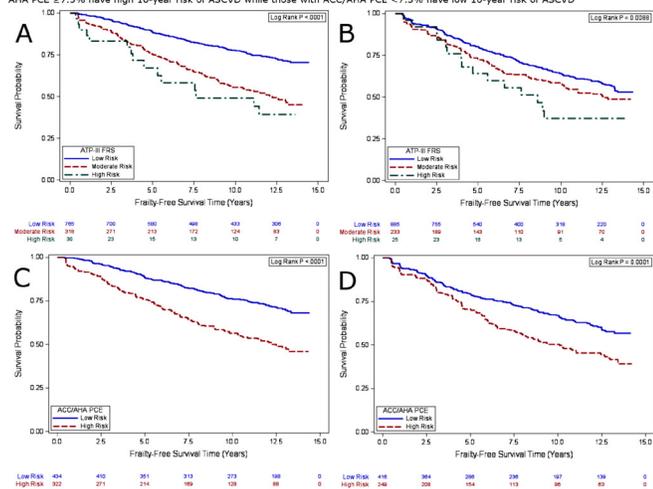
**Methods:** FFP was ascertained in the WIHS during 2004-2006 and 2011-2019, and in the MACS during 2007-2019. FFP score >3 defined frailty. Repeated measures logistic regression, log-rank and Cox proportional hazards regression were performed adjusted for education, income, cholesterol medication use, HCV serostatus, CD4 cell count/ul3, ART use, and HIV viral load.

**Results:** There were 5,554 participants (813 HIV-/2,025 HIV+ women; 1,303 HIV-/1,413 HIV+ men) who had FRS and FFP data at ≥1 visit and 3,630 (494 HIV-/1,443 HIV+ women; 875 HIV-/818 HIV+ men) with PCE available. High risk PCE [adjusted odds ratio(aOR)=1.41(95%CI:1.11-1.80) and aOR=1.43(95% CI:1.20-1.70) but not high risk FRS (aOR=1.23(95%CI:0.46-3.30) and aOR=0.60(95%CI: 0.17-2.15) was associated with higher odds of frailty in HIV- and HIV+ women,

respectively. In men, both high risk FRS (aOR=2.31(95%CI:1.74-3.07) and aOR=2.07(95%CI:1.65-2.60); HIV interaction Plnt=0.63) and high risk PCE (aOR=2.12(95%CI:1.78-2.51) and aOR=1.43(95%CI:1.25-1.63); Plnt=0.0008) were associated with higher odds of frailty in HIV- and HIV+ men, respectively. In log-rank tests (Figure) and adjusted Cox models, high risk FRS [adjusted hazard ratio(aHR)=2.53(95%CI:1.49-4.32) and aHR=1.96(95%CI:1.16-3.31); Plnt=0.95) and high risk PCE aHR=1.80(95%CI:1.39-2.33) and aHR=1.45(95%CI:1.14-1.86); Plnt=0.58) at first ascertainment were both associated with incident frailty in HIV- and HIV+ men, respectively.

**Conclusion:** We found associations of CVD risk with frailty regardless of HIV serostatus. These findings may inform clinical practices of screening for frailty among women and men with and without HIV.

Figure. Kaplan-Meier curves for frailty-free survival: (A) HIV(-) men by ATP-III FRS risk; (B) HIV(+ ) men by ATP-III FRS risk; (C) HIV(-) men by ACC/AHA PCE risk; (D) HIV(+ ) men by ACC/AHA PCE risk. For ATP-III FRS, individuals with >20% estimated risk of CHD within 10 years are high risk; persons with 10-20% risk are moderate risk, and persons with <10% risk are low risk. Individuals with ACC/AHA PCE ≥7.5% have high 10-year risk of ASCVD while those with ACC/AHA PCE <7.5% have low 10-year risk of ASCVD



that included ratings of pain, women with intermediate prescription opioid use had greater odds of being sexual minorities (lesbian or bisexual), unemployed, and were more likely to report benzodiazepine and non-prescription substance use compared to those with minimal use. Similar results were found when comparing chronic to minimal opioid use, but with generally greater magnitude than those observed with intermediate versus minimal use (see Table). Intermediate and chronic prescription opioid use were respectively associated with a 2-fold and 3-fold increased risk of all-cause mortality.

**Conclusion:** Despite federally mandated changes in opioid prescribing guidelines, prescription opioid use in the WHS significantly increased from 2000-2019. Findings underscore the need for non-opioid and non-pharmacologic interventions for chronic pain in sexual minorities and WLWH. Concurrent use of benzodiazepines and non-prescription drugs should also be addressed and treated to reduce risk of mortality.

|   | Intermediate (10-39%) vs. minimal (0-9%) |           | Chronic (40% or greater) vs. minimal (0-9%) |           |
|---|--|-----------|---|-----------|
|   | AOR                                      | 95% CI    | AOR   | 95% CI    |
| History of use crack, powder cocaine, heroin or injection drug use vs. none | 1.92                                     | 1.53-2.44 | 4.03  | 2.93-5.56 |
| Recent crack, powder cocaine, heroin or injection drug use vs. none         | 1.25                                     | 0.95-1.76 | 2.27  | 1.33-3.88 |
| Prescription benzodiazepine use   | 1.87                                     | 1.47-2.38 | 3.22  | 2.36-4.38 |
| HIV seropositive  | 0.82                                     | 0.66-1.00 | 1.56  | 1.06-2.32 |
| Age < 30 years vs. 40-49 years  | 1.08                                     | 0.73-1.59 | 0.30  | 0.18-0.61 |
| Age 30-39 years vs. 40-49 years   | 0.84                                     | 0.71-1.01 | 0.79  | 0.53-1.17 |
| Age 50+ years vs. 40-49 years   | 1.14                                     | 0.98-1.33 | 1.75  | 1.37-2.22 |
| Sexual Minority (Lesbian/Bisexual)  | 1.57                                     | 1.21-2.03 | 1.70  | 1.12-2.59 |
| Not employed  | 1.44                                     | 1.21-1.73 | 2.08  | 1.42-3.04 |
| Quality of life index score*  | 0.53                                     | 0.48-0.58 | 0.92  | 0.87-0.98 |

Note: Bold text indicates statistical significance based on P<0.05 excluding 1.0  
\* Medical Outcomes Study scale (Dunlop et al 1995) - one unit difference in scores  
Also adjusted for sex, baseline prevalence of HIV, completed racial identity, unstable housing and transportation, and  
OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; RTV, Rousso unaccompanied visit

540 SAFETY OF TAF IN PATIENTS WITH A HISTORY OF PROXIMAL RENAL TUBULOPATHY ON TDF

Lucy Campbell<sup>1</sup>, Lisa Hamzah<sup>2</sup>, Amanda Samarawickrama<sup>1</sup>, Alan Winston<sup>3</sup>, Deborah Williams<sup>4</sup>, Rachael Jones<sup>5</sup>, Margarat A. Johnson<sup>6</sup>, Birgit Barbini<sup>1</sup>, Ben Cromarty<sup>7</sup>, Frank A. Post<sup>1</sup>, for the FANTA Trial Team  
<sup>1</sup>King's College Hospital NHS Foundation Trust, London, UK, <sup>2</sup>St George's University of London, London, UK, <sup>3</sup>Imperial College London, London, UK, <sup>4</sup>Brighton and Sussex University Hospitals NHS Trust, Brighton, UK, <sup>5</sup>Chelsea and Westminster Hospital, London, UK, <sup>6</sup>Royal Free Hospital, London, UK, <sup>7</sup>UK Community Advisory Board, London, UK

**Background:** TDF may cause treatment-limiting proximal renal tubulopathy (PRT). We studied the safety of tenofovir alafenamide (TAF) in individuals who had developed PRT while receiving tenofovir disoproxil fumarate (TDF)-containing antiretroviral therapy (ART).

**Methods:** Individuals with HIV RNA <200 c/mL and a history of PRT (confirmed histologically or by ≥2 of: proteinuria [PCR >30 mg/mmol], hypophosphatemia [phosphate <0.64 mmol/L], normoglycemic glycosuria, rapid eGFR decline [>5ml/min/1.73m<sup>2</sup>/year]), clinical resolution upon TDF discontinuation, and not currently receiving TDF or TAF were initiated on emtricitabine(F)/TAF and followed quarterly for 96 weeks. Changes to other components of the ART regimen were allowed. Bone mineral density (BMD) was measured annually by dual X-ray absorptiometry. Renal and bone biomarkers were analysed using multi-level mixed effects linear regression models. The trial was registered under EudraCT 2016-003345-29.

**Results:** 31 individuals were enrolled (mean age 50.1 [SD 16.6] years, 97% male, 13% black ethnicity, median [IQR] time since HIV diagnosis, first ART exposure, and stopping TDF: 19.4 [12.2, 26.2], 12.6 [7.5, 21.0], and 6.9 [5.4, 10.1] years, respectively, and median CD4 count 489 [429, 637] cells/mm<sup>3</sup>); all remained on F/TAF at week 96; none developed glycosuria or PRT; 13 simplified their HIV/HBV regimen. Changes in median values for renal and bone biomarkers are displayed in Fig 1. Participants experienced small declines in creatinine-based eGFR (-2.5 [95%CI -4.2, -0.8]) but not cystatin C-based eGFR (-0.9 [-2.1, 0.4] mL/min/1.73m<sup>2</sup>/year), and increases in RBPCR (6.3 [3.8, 10.7] µg/mmol/year (p<0.0001); albuminuria, fractional excretion of phosphate, markers of bone turnover and BMD remained stable (p>0.1). Five participants (16%) had RBPCR >10xULN (two ongoing from baseline): none had confirmed hypophosphatemia, four had proteinuria (all ongoing and improved from baseline), none had rapid eGFR-cystatin C decline, all had stable FE-P04 and all continued F/TAF post week 96.

**Conclusion:** In individuals with a history of PRT on TDF, 96-weeks of exposure to TAF was not associated with recurrent PRT. RBPCR, a marker of tubular dysfunction, increased over time. A subset of participants had substantial elevations of RBPCR although these were not accompanied by other markers of

539 BEYOND PAIN: PRESCRIPTION OPIOID USE IN THE WOMEN'S INTERAGENCY HIV STUDY

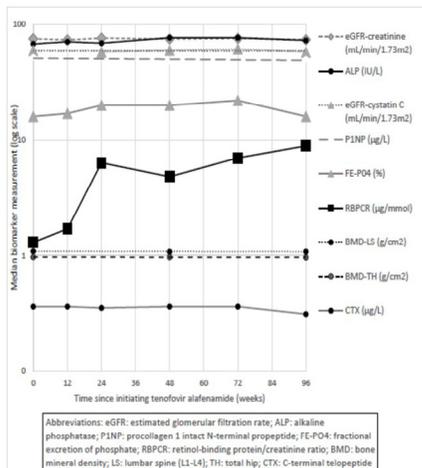
Adam W. Carrico<sup>1</sup>, Lorie Benning<sup>2</sup>, Kathleen Weber<sup>3</sup>, Anjali Sharma<sup>4</sup>, Michael Plankey<sup>5</sup>, Deborah Jones Weiss<sup>1</sup>, Mirjam-Colette Kempf<sup>6</sup>, Bradley Aouizerat<sup>7</sup>, Tracey Wilson<sup>8</sup>, Joel Milam<sup>9</sup>, Adaora Adimora<sup>10</sup>, Gina Wingood<sup>11</sup>, Mardge Cohen<sup>12</sup>  
<sup>1</sup>University of Miami, Miami, FL, USA, <sup>2</sup>John H Stroger Jr Hospital of Cook County, Chicago, IL, USA, <sup>3</sup>Hektoen Institute of Medicine/Cook County Health and Hospitals System, Chicago, IL, USA, <sup>4</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>5</sup>Georgetown University, Washington, DC, USA, <sup>6</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>7</sup>New York University, New York City, NY, USA, <sup>8</sup>State University of New York Downstate Medical Center Downstate Medical Center, Brooklyn, NY, USA, <sup>9</sup>University of Southern California, Los Angeles, CA, USA, <sup>10</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>11</sup>Columbia University, New York, NY, USA, <sup>12</sup>Cook County Health and Hospitals System, Chicago, IL, USA

**Background:** Women are more likely than men to experience chronic pain and use prescription opioids. Less is known about predictors and consequences of prescription opioid use among women living with HIV (WLWH).

**Methods:** 3,826 WLWH or women without HIV enrolled in the Women's Interagency HIV Study (WIHS) and completed bi-annual self-report prescription opioid use assessments from 2000-2019. Cumulative proportion of visits with prescription opioid use was categorized as: minimal (0-9%); intermediate (10-39%); and chronic (40% or greater). Logistic regression examined independent predictors and proportional hazards regression estimated the unadjusted hazard of all-cause mortality, comparing intermediate and chronic prescription opioid use to minimal use.

**Results:** At index visit, most participants were Black (64%), with mean age of 38.9 years and a median annual income of < \$12,000. Women contributed 82,396 person-visits over a median of 10.6 [interquartile range (IQR) = 5.0-17.2] years. The annual prevalence of prescription opioid use significantly increased from 12.6% to 19.3% from 2000-2019 (p < 0.0001). Prescription opioid use was classified as minimal in 75%, intermediate in 16%, and chronic in 9% of women. WLWH had 56% higher odds of chronic prescription opioid use compared to women without HIV. Even after adjusting for quality of life scores

tubular dysfunction. Whilst these data are encouraging, follow up will continue for five years to confirm the long-term safety of F/TAF in this population.



**541 RENAL/BONE OUTCOMES AFTER LONG-ACTING CABOTEGRAVIR + RILPIVIRINE IN ATLAS + ATLAS-2M**

**Paul Benn<sup>1</sup>**, Piotr Budnik<sup>1</sup>, Sterling Wu<sup>2</sup>, Krischan J. Hudson<sup>3</sup>, Yuanyuan Wang<sup>2</sup>, Ronald D'Amico<sup>3</sup>, Conn M. Harrington<sup>3</sup>, Susan L. Ford<sup>4</sup>, Rodica Van Solingen-Ristea<sup>3</sup>, Veerle Van Eygen<sup>3</sup>, Joseph W. Polli<sup>3</sup>, Kimberly Smith<sup>3</sup>, William R. Spreen<sup>3</sup>  
<sup>1</sup>ViiV Healthcare, Brentford, UK, <sup>2</sup>GlaxoSmithKline, Collegeville, PA, USA, <sup>3</sup>ViiV Healthcare, Research Triangle Park, NC, USA, <sup>4</sup>GlaxoSmithKline, Research Triangle Park, NC, USA, <sup>5</sup>Janssen, Beerse, Belgium

**Background:** Intramuscular cabotegravir (CAB) and rilpivirine (RPV) long-acting (LA) has been evaluated in two Phase 3 studies, ATLAS (NCT02951052) and FLAIR (NCT02938520), which demonstrated noninferiority of CAB+RPV LA dosed every 4 weeks (Q4W) to daily oral standard of care (SoC), and the Phase 3b study ATLAS-2M (NCT03299049), demonstrating noninferiority of CAB+RPV LA dosed every 8 weeks (Q8W) to Q4W. Tenofovir disoproxil fumarate (TDF) is associated with renal/bone toxicities and improvements in renal/bone markers have been reported after cessation of TDF regimens. We present data from Week (W) 48 of ATLAS and ATLAS-2M examining changes in renal markers and bone turnover markers.

**Methods:** Data from ATLAS and ATLAS-2M were stratified by baseline (BL) TDF use. Efficacy and safety outcomes including changes in renal markers (urine protein-to-creatinine ratio [UPCR] and urine albumin-to-creatinine ratio [UACR]) and bone turnover markers (bone-specific alkaline phosphatase, osteocalcin, procollagen 1 N-terminal propeptide [P1NP], type 1 collagen C telopeptides [CTX]) were assessed. For ATLAS-2M participants who transitioned from LA therapy in ATLAS, only data from ATLAS were included. W48 efficacy endpoints were proportion with plasma HIV-1 RNA ≥50 c/mL and <50 c/mL. Changes in bone markers were only available for ATLAS participants.

**Results:** In total, 1270 participants were included in the analysis; 665 were receiving TDF at BL and 605 were receiving non-TDF regimens. BL characteristics and outcomes at W48 are presented in Table 1. Within strata, the proportions with HIV-1 RNA ≥50 c/mL and <50 c/mL were comparable across arms. Participants switching from TDF regimens to CAB+RPV LA experienced reductions in UPCR, compared with small increases observed among those switching from or continuing non-TDF regimens. Participants continuing TDF regimens had greater increases in UPCR (mean % UPCR change from BL: TDF: Q8W, -13.2; Q4W, -17.5; SoC, 79.3; non-TDF: Q8W, 10.0; Q4W, 5.4; SoC, 12.0). In ATLAS, there were greater reductions in bone turnover markers in participants switching from TDF to CAB+RPV LA compared with other groups (mean change from BL in P1NP and CTX [µg/L]: TDF: Q4W: -23.7, -0.14; SoC: -12.4, 0.01; non-TDF: Q4W: -8.1, 0.06; SoC: -6.4, 0.07).

**Conclusion:** Participants switching from TDF to CAB+RPV LA experienced improvements in renal markers and bone turnover markers. These results support the therapeutic potential of CAB+RPV LA.

**Table 1. Data From ATLAS/ATLAS-2M at Week 48 Stratified by TDF Use at Baseline**

| Outcome, n (%)                                     | TDF at baseline        |                        |                        | No TDF at baseline     |             |              |
|--|------------------------|------------------------|------------------------|------------------------|-------------|--------------|
|  | Q8W n=151              | Q4W n=333              | SoC n=181              | Q8W n=176              | Q4W n=302   | SoC n=127    |
| Female (sex at birth)                              | 39 (26)                | 106 (32)               | 67 (37)                | 34 (19)                | 68 (23)     | 37 (29)      |
| Age, mean (range)                                  | 43 (21-71)             | 42 (19-68)             | 44 (18-72)             | 43 (20-83)             | 42 (21-74)  | 43 (25-82)   |
| Race   |                        |                        |                        |                        |             |              |
| Black/African American                             | 31 (21)                | 75 (23)                | 63 (35)                | 26 (15)                | 32 (11)     | 14 (11)      |
| White  | 102 (68)               | 217 (65)               | 104 (57)               | 136 (77)               | 253 (84)    | 103 (81)     |
| Other  | 18 (12)                | 41 (12)                | 14 (8)                 | 14 (8)                 | 17 (6)      | 10 (8)       |
| Baseline UACR, mean (SD)                           | 1.4 (2.4)              | 1.4 (2.7)              | 2.4 (9.8)              | 1.2 (2.9)              | 0.8 (1.3)   | 1.5 (4.9)    |
| Baseline UPCR, mean (SD)                           | 12.6 (9.7)             | 11.9 (9.4)             | 14.6 (18.0)            | 8.3 (6.1)              | 8.3 (5.7)   | 8.7 (6.9)    |
| eGFR group at baseline, mL/min/1.73 m <sup>2</sup> |                        |                        |                        |                        |             |              |
| ≥90  | 100 (66)               | 249 (75)               | 140 (77)               | 109 (62)               | 203 (67)    | 94 (74)      |
| 60-89  | 50 (33)                | 81 (24)                | 40 (22)                | 65 (37)                | 95 (31)     | 28 (22)      |
| 44-59  | 1 (<1)                 | 2 (<1)                 | 1 (<1)                 | 2 (1)                  | 4 (1)       | 5 (4)        |
| <44  | 0                      | 1 (<1)                 | 0                      | 0                      | 0           | 0            |
| Proteinuria at baseline                            |                        |                        |                        |                        |             |              |
| 0  | 129 (85)               | 294 (88)               | 148 (82)               | 164 (93)               | 285 (94)    | 120 (94)     |
| +  | 3 (2)                  | 10 (3)                 | 10 (6)                 | 3 (2)                  | 5 (2)       | 2 (2)        |
| ++   | 0                      | 1 (<1)                 | 1 (<1)                 | 0                      | 0           | 0            |
| +++  | 17 (11)                | 21 (6)                 | 16 (9)                 | 8 (5)                  | 9 (3)       | 4 (3)        |
| Missing  | 2 (1)                  | 7 (2)                  | 6 (3)                  | 1 (<1)                 | 3 (<1)      | 1 (<1)       |
| HIV-1 RNA ≥50 c/mL at Week 48                      | 3 (2.0)                | 2 (0.6)                | 1 (0.6)                | 2 (1.1)                | 8 (2.6)     | 2 (1.6)      |
| HIV-1 RNA <50 c/mL at Week 48                      | 142 (94.0)             | 309 (92.8)             | 174 (96.1)             | 164 (93.2)             | 276 (91.4)  | 120 (94.5)   |
| Drug-related AEs                                   | 130 (86)               | 280 (84)               | 4 (2)                  | 142 (81)               | 247 (82)    | 4 (3)        |
| Drug-related AEs leading to withdrawal             | 1 (<1)                 | 9 (3)                  | 1 (<1)                 | 5 (3)                  | 9 (3)       | 0            |
| UACR, mean (SD) % change from baseline*            | 33.3 (211.1)           | 18.2 (119.9)           | 17.2 (81.6)            | 23.5 (76.0)            | 30.3 (99.6) | 28.1 (152.4) |
| UPCR, mean (SD) % change from baseline†            | -13.2 (43.3)           | -17.5 (40.2)           | 79.3 (873.7)           | 10.0 (59.9)            | 5.4 (49.2)  | 12.0 (40.5)  |
| Bone markers, mean (SD) change from baseline       | TDF at baseline        |                        | No TDF at baseline     |                        |             |              |
|  | Q4W (ATLAS only) n=196 | SoC (ATLAS only) n=181 | Q4W (ATLAS only) n=112 | SoC (ATLAS only) n=127 |             |              |
| Bone-specific alkaline phosphatase (µg/L)‡         | -4.12 (5.62)           | -0.61 (4.20)           | -0.84 (3.27)           | -0.23 (2.76)           |             |              |
| Osteocalcin (µg/L)‡                                | -3.71 (7.02)           | -1.94 (4.80)           | -2.53 (6.45)           | -0.99 (6.33)           |             |              |
| Procollagen 1 N-terminal propeptide (µg/L)‡        | -23.7 (27.3)           | -12.4 (21.4)           | -8.1 (19.5)            | -6.4 (17.5)            |             |              |
| Type 1 collagen C-telopeptides (µg/L)‡             | -0.14 (0.25)           | 0.01 (0.27)            | 0.08 (0.21)            | 0.07 (0.24)            |             |              |

AE, adverse event; eGFR, estimated glomerular filtration rate; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation; SoC, standard of care; TDF, tenofovir disoproxil fumarate; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.  
 \*Prior TDF - Week 48: Q8W, n=107; Q4W, n=220; SoC, n=121. No prior TDF - Week 48: Q8W, n=113; Q4W, n=193; SoC, n=84.  
 †Prior TDF - Week 48: Q4W, n=178; SoC, n=170. No prior TDF - Week 48: Q4W, n=99; SoC, n=118.  
 ‡Prior TDF - Week 48: Q4W, n=179; SoC, n=172. No prior TDF - Week 48: Q4W, n=99; SoC, n=120.  
 §Prior TDF - Week 48: Q4W, n=177; SoC, n=172. No prior TDF - Week 48: Q4W, n=102; SoC, n=119.  
 ¶Prior TDF - Week 48: Q4W, n=175; SoC, n=163. No prior TDF - Week 48: Q4W, n=101; SoC, n=114.

**542 HIV IS ASSOCIATED WITH A HIGHER RATE OF COVID-19 DIAGNOSIS BUT NO ADVERSE OUTCOMES**

**Michael E. Tang<sup>1</sup>**, Thaidra Gaufin<sup>1</sup>, Ryan Anson<sup>1</sup>, Edward R. Cachay<sup>1</sup>  
<sup>1</sup>University of California San Diego, San Diego, CA, USA

**Background:** Most available data on COVID-19 among persons with HIV (PWH) focuses on hospitalized patients, while COVID-19 risk among PWH relative to the general population remains inconclusive.

**Methods:** Using a retrospective comparative cohort analysis, we included all adults with established primary care service at UC San Diego who underwent testing for COVID-19 from March to July 2020. We dichotomized the cohort into two groups, PWH and non-PWH. We used bivariate analyses to compare group differences using a clinical hierarchical order, including COVID-19 diagnosis, hospitalization, intensive care unit (ICU) admission, intubation, and death. Logistic regression models for each hierarchical clinical outcome included pre-specified covariates (demographics, diabetes mellitus, and obesity) and additional covariates at a 0.20 threshold via backward model selection. Interactions between HIV status and other covariates were included at the 0.05 threshold. Additional covariates included insurance type, hypertension, cardiovascular disease, chronic kidney, lung, liver disease, rheumatologic disease, cancer history, ACE inhibitor or angiotensin II receptor blocker use, and active tobacco, alcohol or illicit drug use, and history of mental health disorder.

**Results:** Of 235609 participants, 3609 were PWH and 232000 non-PWH. Of them, 22% of PWH and 6% of non-PWH were tested for COVID-19. The PWH group had a higher proportion of younger individuals (76% vs 57%), males (85% vs 39%), non-whites (42 vs 35%), and a history of mental illness (58 vs 29%) than the non-PWH group. Of those tested, 7% of PWH and 2% of non-PWH tested positive for COVID-19. The adjusted odds ratio of COVID-19 diagnosis for HIV vs non-HIV was 4.32 (95% CI 3.09-6.04). No significant differences were observed for PWH compared to non-PWH in the proportion of patients hospitalized (15% vs 15%), admitted to ICU (10% vs 7%), requiring inotropic support (3% vs 4%), or died (3% vs 3%) but PWH required mechanical ventilation more frequently than those non-PWH (8% vs. 3%). HIV was not a significant predictor of hospitalization, ICU admission, or mortality in any

models (see table); however, the limited number of events decreased the statistical power.

**Conclusion:** In our cohort, PWH were tested and diagnosed more frequently than those without HIV for COVID-19. PWH had an increased risk of becoming infected with COVID-19, even when adjusted for demographics and comorbidities. HIV status did not affect hospitalization, ICU admission, or mortality.

**Table 1: Adjusted Odds Ratios (95%CI) for outcome by predictor**

| Predictor                 | Diagnosis           | Hospitalization      | ICU                  | Intubation           | Death                |
|---------------------------|---------------------|----------------------|----------------------|----------------------|----------------------|
| HIV                       | 4.32<br>(3.09-6.04) | 0.44<br>(0.13-1.56)  | 2.89<br>(0.90-9.28)  | 1.51<br>(0.37-6.18)  | 7.64<br>(0.72-80.55) |
| Age (per 10 years)        | 0.78<br>(0.73-0.85) | 2.43<br>(1.75-3.38)  | 2.03<br>(1.45-2.84)  | NS                   | 2.96<br>(1.38-6.33)  |
| Gender (Male vs Female)   | 1.27<br>(0.99-1.61) | 1.95<br>(0.79-4.81)  | NS                   | 4.55<br>(0.91-22.81) | 0.21<br>(0.03-1.47)  |
| Race (Non-white vs White) | 1.61<br>(1.28-2.03) | 2.56<br>(1.05-6.25)  | NS                   | 2.45<br>(0.62-9.64)  | NS                   |
| Diabetes                  | 1.63<br>(1.14-2.32) | NS                   | 2.97<br>(1.08-8.15)  | 4.93<br>(1.32-18.48) | NS                   |
| Obesity                   | 1.60<br>(1.25-2.04) | NS                   | NS                   | NS                   | 7.60<br>(1.05-54.95) |
| Smoking                   | 0.51<br>(0.29-0.90) | NS                   | NS                   | NS                   | NS                   |
| Alcohol                   | NS                  | 0.42<br>(0.16-1.08)  | NS                   | NS                   | NS                   |
| Drug use                  | NS                  | 3.37<br>(0.92-12.39) | NS                   | NS                   | NS                   |
| Hypertension              | NS                  | 2.26<br>(0.87-5.87)  | NS                   | 6.24<br>(1.28-30.54) | NS                   |
| Heart Disease             | NS                  | 0.34<br>(0.08-1.51)  | NS                   | NS                   | NS                   |
| Pulmonary disease         | NS                  | 3.55<br>(1.11-11.37) | NS                   | NS                   | NS                   |
| Rheumatic disease         | 2.14<br>(1.12-4.10) | NS                   | NS                   | NS                   | NS                   |
| Cirrhosis                 | 0.52<br>(0.28-0.96) | NS                   | NS                   | NS                   | NS                   |
| Chronic Kidney Disease    | NS                  | 3.55<br>(0.70-18.04) | NS                   | NS                   | 6.32<br>(0.80-49.75) |
| Cancer                    | 0.76<br>(0.49-1.17) | 5.20<br>(1.42-19.01) | 4.26<br>(1.27-14.26) | NS                   | 7.98<br>(1.13-56.41) |
| Mental health             | 0.73<br>(0.56-0.95) | 1.90<br>(0.77-4.67)  | NS                   | NS                   | NS                   |

NS: Not significant, ICU: Intensive Care Unit  
 HIV, Age, Gender, Race, Diabetes, and Obesity are included in all models as pre-specified predictors regardless of p value  
 0.20 threshold via backwards model selection (BMS) for main effects  
 0.05 threshold via BMS for interactions with HIV

with COVID-19 was associated with: CD4+ count  $\leq 350$  (aRR 1.77; 95% CI 1.05, 2.98); age  $\geq 60$  (aRR 2.0; 95% CI 1.13, 3.54); pre-existing kidney disease with eGFR  $< 60$  (aRR 1.76; 95% CI 0.99, 3.13); and BMI  $\geq 30$  (aRR 1.96; 95% CI 1.02, 3.78) (Table).

**Conclusion:** The population frequency of COVID-19 detected in PWH was 1.4%, likely an underestimate of the true frequency of SARS-CoV-2 infection and COVID-19 disease due to evolving testing availability and access over time. A higher proportion of PWH with COVID-19 were Black or Hispanic, in excess of the overrepresentation of people of color with HIV compared to the general population. PWH with decreased eGFR, low CD4+ count, and obesity had greater risk of more severe COVID-19 disease. Our results highlight disparities in risk of COVID-19 acquisition among PWH in the US and indicate additional vigilance in screening and monitoring of COVID-19 among PWH with these characteristics. The expected accrual of additional COVID-19 cases will allow more precise evaluation of the impact of comorbidities.

**Table.** Characteristics of PWH in the CNICS Cohort with COVID-19 by hospitalization status and relative risk of hospitalization for selected characteristics.

| Characteristic <sup>a</sup>                       | Total     | Not Hospitalized | Hospitalized | RR <sup>b</sup>  | 95% CI     | p-value |
|---|-----------|------------------|--------------|--|------------|---------|
| <b>N (% of total)</b>                             | 198       | 160 (81%)        | 38 (19%)     |  |            |         |
| <b>Female</b>                                     | 54 (27%)  | 41 (26%)         | 13 (34%)     | 1.02   | 0.55, 1.88 | 0.962   |
| <b>Age (years)</b>                                |           |                  |              | RR ( $\geq 60$ vs. $< 60$ )                            |            |         |
| <30   | 18 (9%)   | 16 (10%)         | 2 (5%)       |  |            |         |
| 30-39   | 39 (20%)  | 34 (21%)         | 5 (13%)      | ref  |            |         |
| 40-49   | 39 (20%)  | 32 (20%)         | 7 (18%)      |  |            |         |
| 50-59   | 54 (27%)  | 44 (28%)         | 10 (26%)     |  |            |         |
| $\geq 60$   | 48 (24%)  | 34 (21%)         | 14 (37%)     | 2.00   | 1.13, 3.54 | 0.017   |
| <b>Race/ethnicity</b>                             |           |                  |              | RR (Black vs. non-Black)                               |            |         |
| Black   | 104 (53%) | 77 (48%)         | 27 (71%)     | 1.42   | 0.69, 2.91 | 0.336   |
| White   | 42 (21%)  | 39 (24%)         | 3 (8%)       |  |            |         |
| Hispanic  | 45 (23%)  | 38 (24%)         | 7 (18%)      | ref  |            |         |
| Other   | 7 (4%)    | 6 (4%)           | 1 (3%)       |  |            |         |
| <b>HIV transmission risk factor</b>               |           |                  |              | RR (heterosexual vs. other risk factors)               |            |         |
| Heterosexual                                      | 65 (33%)  | 44 (28%)         | 21 (55%)     | 1.71   | 0.94, 3.13 | 0.079   |
| MSM   | 101 (51%) | 88 (55%)         | 13 (34%)     |  |            |         |
| IDU   | 24 (12%)  | 21 (13%)         | 3 (8%)       | ref  |            |         |
| Other   | 8 (4%)    | 7 (4%)           | 1 (3%)       |  |            |         |
| <b>Lowest CD4+ count (cells/mm<sup>3</sup>)</b>   |           |                  |              | RR ( $\leq 350$ vs. $> 350$ cells/mm <sup>3</sup> )    |            |         |
| <200  | 91 (47%)  | 71 (45%)         | 20 (54%)     |  |            |         |
| 200-349   | 47 (24%)  | 41 (26%)         | 6 (16%)      | 1.39   | 0.73, 2.62 | 0.316   |
| 350-499   | 24 (12%)  | 17 (11%)         | 7 (19%)      |  |            |         |
| $\geq 500$  | 32 (17%)  | 28 (18%)         | 4 (11%)      | ref  |            |         |
| <b>CD4+ count (cells/mm<sup>3</sup>)</b>          |           |                  |              | RR ( $\leq 350$ vs. $> 350$ cells/mm <sup>3</sup> )    |            |         |
| <200  | 17 (9%)   | 9 (6%)           | 8 (21%)      | 1.77   | 1.05, 2.98 | 0.032   |
| 200-349   | 25 (13%)  | 21 (14%)         | 4 (11%)      |  |            |         |
| 350-499   | 26 (14%)  | 24 (16%)         | 2 (5%)       | ref  |            |         |
| $\geq 500$  | 120 (64%) | 96 (64%)         | 24 (63%)     |  |            |         |
| <b>ART status</b>                                 | 192 (97%) | 156 (98%)        | 36 (95%)     | — <sup>c</sup>   |            |         |
| <b>Undetectable viral load (&lt;50 copies/mL)</b> | 158 (81%) | 126 (80%)        | 32 (84%)     | — <sup>c</sup>   |            |         |
| <b>Hepatitis C virus</b>                          | 26 (13%)  | 20 (13%)         | 6 (16%)      | 1.05   | 0.48, 2.33 | 0.900   |
| <b>Diabetes</b>                                   | 48 (24%)  | 33 (21%)         | 15 (40%)     | 1.49   | 0.85, 2.61 | 0.166   |
| <b>Anti-hypertensive use</b>                      | 79 (42%)  | 60 (40%)         | 19 (51%)     | 1.30   | 0.74, 2.28 | 0.365   |
| <b>Ever smoker</b>                                | 70 (35%)  | 62 (39%)         | 8 (21%)      | 0.54   | 0.26, 1.11 | 0.092   |
| <b>eGFR (mL/min/1.73 m<sup>2</sup>)</b>           |           |                  |              | RR ( $< 60$ vs. $\geq 60$ mL/min/1.73 m <sup>2</sup> ) |            |         |
| $\geq 60$   | 165 (86%) | 139 (89%)        | 26 (70%)     | ref  |            |         |
| $< 60$  | 28 (15%)  | 17 (11%)         | 11 (30%)     | 1.76   | 0.99, 3.13 | 0.055   |
| <b>BMI (kg/m<sup>2</sup>)</b>                     |           |                  |              | RR ( $< 30$ vs. $\geq 30$ kg/m <sup>2</sup> )          |            |         |
| <30   | 102 (55%) | 91 (60%)         | 11 (31%)     | ref  |            |         |
| $\geq 30$   | 84 (45%)  | 60 (40%)         | 24 (69%)     | 1.96   | 1.02, 3.78 | 0.044   |
| <b>COPD</b>                                       | 12 (6%)   | 9 (6%)           | 3 (8%)       | — <sup>c</sup>   |            |         |

Data presented as n (%) unless otherwise noted. Percent may not add to 100 due to rounding.  
 Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk.  
<sup>a</sup> Most recent value at least two weeks prior to the COVID-19 diagnosis.  
<sup>b</sup> Relative risk regression models using a Poisson distribution and adjusted for demographic and clinical characteristics using disease risk scores. Disease risk score included age, sex, race/ethnicity, site, and ever smoker status.  
<sup>c</sup> Insufficient variation in data to estimate relative risk.

**543 COVID-19 CASES & HOSPITALIZATIONS IN A US MULTISITE COHORT OF PEOPLE WITH HIV**

**Adrienne E. Shapiro<sup>1</sup>**, Rachel A. Bender Ignacio<sup>1</sup>, Bridget M. Whitney<sup>1</sup>, Joseph A. Delaney<sup>2</sup>, Robin M. Nance<sup>3</sup>, H. Nina Kim<sup>1</sup>, Jeanne C. Keruly<sup>3</sup>, Greer Burkholder<sup>4</sup>, Sonia Napravnik<sup>5</sup>, Kenneth H. Mayer<sup>6</sup>, Allison R. Weber<sup>7</sup>, Heidi Crane<sup>1</sup>, Mari M. Kitahata<sup>1</sup>, Edward R. Cachay<sup>8</sup>, for the CNICS Investigator Team  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>University of Manitoba, Winnipeg, Canada, <sup>3</sup>Johns Hopkins School of Medicine, Baltimore, MD, <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>Fenway Health, Boston, MA, USA, <sup>7</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>8</sup>University of California San Diego, San Diego, CA, USA

**Background:** COVID-19 outcomes among people with HIV (PWH) remain inconclusive. We characterized all cases of COVID-19 identified in a long-term multi-site cohort of PWH, as well as factors associated with increasing severity of COVID-19 during the early months of the COVID-19 pandemic.

**Methods:** We examined all PWH with SARS-CoV-2 infection and COVID-19 disease identified from laboratory testing data (RT-PCR, antigen test results) and ICD-10 codes March-July 2020 from seven sites in the CFAR Network of Integrated Clinical Systems (CNICS) cohort. Cases were verified by medical record review. We evaluated predictors of increased disease severity, indicated by hospitalization. Relative risks were estimated using Poisson regression, adjusted for clinical and demographic characteristics using disease risk scores.

**Results:** Among 13,862 PWH in care (20% female, median age 52 (IQR 40-59), 58% Black or Hispanic race/ethnicity), 198 COVID-19 cases were detected during the study period. A higher proportion of PWH with COVID-19 were female (27%), Black or Hispanic (76%), and had BMI  $\geq 30$  (45%). No significant differences in CD4+ count (current or lowest) were seen between PWH with and without COVID-19. We found evidence suggesting more unstable housing among COVID-19 cases compared to non-cases (14% vs. 9%). Among PWH with COVID-19, 38 (19%) were hospitalized, 10 (5%) required intensive care, 8 (4%) received invasive mechanical ventilation, and 4 (2%) died. Hospitalization among PWH

**544 COVID-19 IN HOSPITALIZED HIV-POSITIVE AND HIV-NEGATIVE PATIENTS: A MATCHED STUDY**

**Cristina Díez<sup>1</sup>**, Jorge Del Romero-Raposos<sup>2</sup>, Rafael Mican<sup>3</sup>, Juan Lopez<sup>1</sup>, Ana Delgado-Hierro<sup>3</sup>, Lucio Jesús F. García-Fraile<sup>4</sup>, María Saumoy<sup>5</sup>, Gloria Samperiz<sup>6</sup>, Sonia Calzado<sup>7</sup>, Jose R. Arribas<sup>3</sup>, Santiago Moreno<sup>8</sup>, Juan González-García<sup>3</sup>, Inmaculada Jarrín<sup>2</sup>, Juan Berenguer<sup>1</sup>, for the CoRIS Research Group  
<sup>1</sup>Hospital General Universitario Gregorio Marañón, Madrid, Spain, <sup>2</sup>Instituto de Salud Carlos III, Madrid, Spain, <sup>3</sup>La Paz University Hospital, Madrid, Spain, <sup>4</sup>Hospital Universitario de La Princesa, Madrid, Spain, <sup>5</sup>Hospital Universitario de Bellvitge, Barcelona, Spain, <sup>6</sup>Hospital Universitario Miguel Servet, Zaragoza, Spain, <sup>7</sup>Hospital Universitario Parc Tauli, Sabadell, Spain, <sup>8</sup>Hospital Ramón y Cajal, Madrid, Spain

**Background:** We compared the characteristics and clinical outcomes of hospitalized patients with COVID-19 with and without HIV infection (HIV-pos and HIV-neg) in Spain during the first wave of the pandemic.

**Methods:** HIV-pos were identified by reviewing clinical records and laboratory registries of 10,922 patients in active-follow-up within the Spanish HIV Research Network (CoRIS) up to June 30, 2020. Each HIV-pos was matched with 5 HIV-neg of the same age and sex randomly selected from COVID-19@Spain, a multicenter cohort of 4,035 patients hospitalized with PCR confirmed COVID-19 in Spain (Clin Microbiol Infect 2020;26:1525-36). Data were collected with the ISARIC-WHO Core case report form (<https://isaric.org/document/covid-19-crf/>). The COVID-19 SEIMC score (predictive of 30-day mortality), based on age, sex, dyspnea, O2 saturation, neutrophil-to-lymphocyte ratio, and estimated glomerular filtration rate, was calculated at admission in all patients (ESCMID Conference on Coronavirus Disease, 2020, Abstract#00513). Outcomes included the need for mechanical ventilation and all-cause in-hospital mortality.

**Results:** Forty-five patients with PCR confirmed COVID-19 were identified in CoRIS, 21 of which were hospitalized. A total of 105 age/sex-matched controls were selected from COVID-19@Spain. The median age in both groups was 53 (Q1-Q3, 46-56) years, and 90.5% were men. In HIV-pos, 19.1% were IDUs, 95.2% were on ART, 94.4% had HIV-RNA < 50 copies/mL, and the median (Q1-Q3) CD4+ count was 595 (349 – 798) cells/mm<sup>3</sup>. No statistically significant differences were found between groups in number and type of comorbidities, presenting signs and symptoms, laboratory parameters, and radiology findings. The median (Q1-Q3) COVID-19 SEIMC score on admission was 4 (2 – 7) and 5 (3 - 7) in HIV-pos and HIV-neg, respectively; P=.890. Corticosteroids were administered to 33.3% and 27.4% HIV-pos and HIV-neg, respectively; P=.58. Remdesivir was administered to 0 and 2.9% of HIV-pos and HIV-neg, respectively; P=.426. During admission, 9.5% HIV-pos and 23.3% HIV-neg underwent mechanical ventilation; P=.158. In-hospital mortality was 9.5% in HIV-pos and 11.4% in HIV-neg; P=.800.

**Conclusion:** Our findings suggest that well-controlled HIV infection does not modify the clinical presentation or worsen clinical outcomes in patients hospitalized with COVID-19.

**Table.** Characteristics and outcomes of HIV-pos and HIV-neg hospitalized with COVID-19

| Variable                                     | HIV-pos<br>N = 21 | Age/sex-matched<br>HIV-neg<br>N = 105 | P     |
|--|-------------------|---------------------------------------|-------|
| Chest X-ray on admission – No./with data (%) | 20/21 (95.2)      | 100/105 (95.2)                        | >.999 |
| Presence of lung infiltrates                 | 18 (90.0)         | 86 (86.0)                             | .631  |
| Comorbidities – No./with data (%)            | 21/21 (100.0)     | 91/105 (86.7)                         | .124  |
| None   | 8 (38.1)          | 36 (39.8)                             | .782  |
| 1-2  | 9 (42.9)          | 43 (47.3)                             |       |
| ≥3   | 4 (19.0)          | 12 (13.2)                             |       |
| COVID-19 SEIMC Score # – No./with data (%)   | 15/21 (71.4)      | 85/105 (81.0)                         | .377  |
| Median (Q1-Q3)                               | 4 (2 – 7)         | 5 (3 - 7)                             | .996  |
| Corticosteroids – No./with data (%)          | 7/21 (33.3)       | 28/102 (27.4%)                        | .586  |
| Remdesivir – No./with data (%)               | 0/21              | 3/102 (2.9)                           | .426  |
| Mechanical ventilation – No./with data (%)   | 2/21 (9.5)        | 24/103 (23.3)                         | .158  |
| In-hospital mortality – No./with data (%)    | 2/21 (9.5)        | 12/105 (11.4)                         | .800  |

\*30-d mortality risk: 0-2 low (0-2.1%), 3-5 moderate (4.7-6.3%), 6-8 high (10.6 – 19.5%), 9-30 very high (27.7 – 100%)

**545 CHARACTERISTICS AND OUTCOMES OF COVID-19-RELATED HOSPITALIZATION AMONG PLWH**

**Roberta Gagliardini<sup>1</sup>,** Patrizia Lorenzini<sup>1</sup>, Alessandra Vergori<sup>1</sup>, Stefania Cicalini<sup>1</sup>, Carmela Pinnetti<sup>1</sup>, Valentina Mazzotta<sup>1</sup>, Annalisa Mondì<sup>1</sup>, Emanuele Nicastri<sup>1</sup>, Nicola Petrosillo<sup>1</sup>, Fabrizio Palmieri<sup>1</sup>, Gianpiero D’Offizi<sup>1</sup>, Enrico Girardi<sup>1</sup>, Giuseppe Ippolito<sup>1</sup>, Francesco Vaia<sup>1</sup>, Andrea Antinori<sup>1</sup>  
<sup>1</sup>IRCCS Lazzaro Spallanzani, Rome, Italy

**Background:** There is conflicting evidence on how HIV influences COVID19 infection. Aim of this study was to compare characteristics at presentation and clinical outcomes of people living with HIV (PLWH) versus HIV negative patients (non-PLWH) hospitalized with COVID-19.

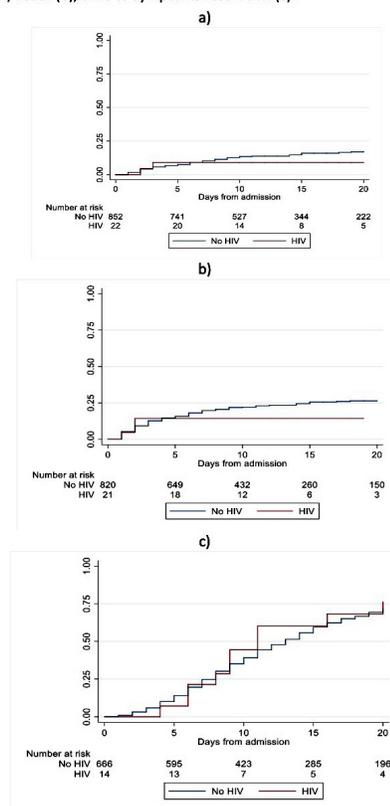
**Methods:** Patients ≥18 years with SARS-CoV-2 infection, defined as positive RT-PCR from nasal/oropharyngeal swab or positive serology, admitted at L. Spallanzani Institute (Italy) were included. Primary endpoint: time to invasive ventilation/death. Secondary endpoints: time to ventilation/death, time to symptoms resolution (resolution of fever or waning from oxygen). In order to control for measured confounders, Cox regression model was used.

**Results:** A total of 905 hospitalized patients were included in the analysis (22 [2.4%] PLWH, 883 non-PLWH): 65% males, 66% with at least one comorbidity, median PaO<sub>2</sub>/FiO<sub>2</sub> at admission 343 mmHg (260-405). PLWH were slightly younger (56 vs 62 years, p=0.057), less likely with pneumonia (59% vs 87%, p<0.001) and with PaO<sub>2</sub>/FiO<sub>2</sub> <300 mmHg at admission (10% vs 31%, p=0.088), with less alterations in lymphocytes (1505 cells/mm vs 1170, p=0.025) and D-dimer (473 ng/mL vs 661, p=0.015) compared with non-PLWH.

Symptoms at presentation were similar in the two groups apart from headache and myalgia that were more frequent in PLWH (both p<0.001). Among PLWH, nadir CD4 was 80 (33-284) cells/μl, CD4 at COVID19 diagnosis 350 cells/μl (138-515), all of them were on antiretroviral therapy and 94% had HIV-1 RNA < 50 copies/mL. The cumulative probability of invasive ventilation/death at day 14 was 9.1% (95% CI 2.4-31.7) in PLWH versus 14.7% (12.3-17.6) in non-PLWH (p=0.492). The cumulative probability of non-invasive or invasive ventilation/death at day 14 was 14.3% (4.8-38.0) in PLWH versus 24.4% (21.4-27.8) in non-PLWH (p=0.372). Following adjustment for age, gender, comorbidities, PaO<sub>2</sub>/FiO<sub>2</sub> and pneumonia at admission, adjusted hazard ratio (aHR) of mechanical ventilation/death of PLWH was 0.95 (95% CI 0.13-6.98, p=0.958) versus non-PLWH; similarly, aHR of non-invasive or invasive ventilation/death of PLWH was 1.05 (95% CI 0.26-4.28, p=0.947). The probability of symptoms resolution at day 14 was similar in the two groups (aHR 1.16; 0.65-2.09; p=0.614).

**Conclusion:** A less severe presentation and no difference in clinical outcomes with Covid-19 even in the adjusted models were observed in PLWH compared to non-PLWH, but further investigations are warranted due to the small sample size of HIV+ population.

**Figure:** Kaplan-Meier estimates of time to invasive ventilation/death (a), time to non-invasive or invasive ventilation/death (b), time to symptoms resolution (c).



**546 RISK FACTORS FOR HOSPITALIZATION IN PEOPLE WITH HIV AND COVID-19**

**Lauren K. Barbera<sup>1</sup>,** Kevin F. Kamis<sup>2</sup>, Mona H. Abdo<sup>1</sup>, Katie A. Kozacka<sup>1</sup>, Edward M. Gardner<sup>3</sup>, Samantha MaWhinney<sup>1</sup>, Sarah E. Rowan<sup>2</sup>, Kristine Erlandson<sup>1</sup>  
<sup>1</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>2</sup>Denver Public Health, Denver, CO, USA, <sup>3</sup>Denver Health Medical Center, Denver, CO, USA

**Background:** People living with HIV are thought to be at higher risk for poor outcomes (including higher hospitalization and mortality rates) from SARS-CoV-2 (COVID-19) infection. Whether risk is linked to HIV-related factors, demographics or comorbid burden is unclear. We examine risk factors and outcomes of those living with HIV who acquired COVID-19 and received care within two large healthcare systems in Denver, CO.

**Methods:** A retrospective analysis was conducted for all individuals with HIV diagnosed with COVID-19 at the two largest Colorado HIV care centers between 1 March and 31 October 2020. COVID-19 diagnosis required a positive PCR result; HIV diagnosis was extracted from the medical record. Risk factors for

hospitalization and longer hospital length of stay (LOS) were examined and compared via univariate and multivariable analysis.

**Results:** Among 94 patients, 81% were male, with a mean age of 46 (SD 13.5) years. The majority had HIV-1 RNA levels <50 copies/mL (87%) and CD4 count >500 cells/mm<sup>3</sup> (55%). Most (75%) had ≥1 comorbidity; 64% were overweight or obese. 39% of patients were admitted to the hospital (17% to intensive care). Increased odds of hospitalization were associated with increased age, lower CD4 count, and increased number of comorbidities (including diabetes, hypertension, chronic kidney disease, chronic pulmonary disease, cardiac disease, mental health concerns, and obesity) (Table). In multivariable analyses, only lower CD4 count (OR 1.28) and comorbidity count (OR 1.62) remained significant. Among hospitalized patients, longer LOS was univariately associated with age (52% longer LOS per 10 year age increase [95% CI 16,101%],  $p=0.004$ ) but not CD4 count (-8%, [95% CI -18, 5%] % change in LOS per 100 cell/mm<sup>3</sup> increase,  $p=0.21$ ), HIV-1 viral load ≥200 copies/mL (-33% [95% CI -77, 90%],  $p=0.44$ ), or comorbidity count (10% [95% CI -17, 43%] change in LOS per additional comorbidity,  $p=0.49$ ). Sensitivity analyses excluding 9 patients hospitalized for non-COVID reasons provided similar findings.

**Conclusion:** Lower CD4 count was associated with an increased risk of hospitalization among patients with concurrent HIV and COVID-19, suggesting that successful HIV treatment remains a key component to decreasing HIV-related morbidity.

Table: Odds of Hospitalization among 94 Adults with HIV and COVID-19

| Variable   | Univariate         |         | Multivariable*    |         |
|--|--------------------|---------|-------------------|---------|
|  | OR (95% CI)        | P-value | OR (95% CI)       | P-value |
| Age (per 10-year increase)                         | 1.54 (1.09, 2.17)  | 0.02    | 1.32 (0.90, 1.95) | 0.16    |
| Sex (ref=Male)                                     |                    |         |                   |         |
| Female   | 1.03 (0.36, 2.96)  | 0.95    |                   |         |
| Race/ethnicity (ref=White)                         |                    |         |                   |         |
| Other  | 2.30 (0.97, 5.45)  | 0.06    |                   |         |
| Primary Language (ref=English)                     |                    |         |                   |         |
| Spanish  | 0.33 (0.09, 1.25)  | 0.07    |                   |         |
| Other  | 2.84 (0.25, 32.70) | 0.21    |                   |         |
| BMI (ref=Underweight or normal)                    |                    |         |                   |         |
| Overweight or obese                                | 0.66 (0.28, 1.58)  | 0.35    |                   |         |
| CD4 count (per 100 cells/mm <sup>3</sup> decrease) | 1.32 (1.11, 1.56)  | 0.001   | 1.28 (1.07, 1.53) | 0.008   |
| HIV-1 RNA (ref= ≤200 copies/mL)                    |                    |         |                   |         |
| >200 copies/mL                                     | 2.55 (0.74, 8.78)  | 0.14    |                   |         |
| Tobacco Use  |                    |         |                   |         |
| Current smoker (vs nonsmoker)                      | 0.97 (0.29, 3.28)  | 0.46    |                   |         |
| Former smoker (vs nonsmoker)                       | 2.30 (0.86, 6.15)  | 0.10    |                   |         |
| Comorbidity Count                                  | 1.77 (1.23, 2.56)  | 0.002   | 1.62 (1.07, 2.47) | 0.02    |

\*Multivariable model included age, CD4 count, and comorbidity count

## 547 COMORBIDITY BURDEN IS ASSOCIATED WITH HOSPITALIZATION FOR COVID-19 AMONG PWH

**Caitlin A. Moran**<sup>1</sup>, Nora Oliver<sup>2</sup>, Brittany V. Szabo<sup>3</sup>, Lauren F. Collins<sup>1</sup>, Minh L. Nguyen<sup>1</sup>, Sarita Shah<sup>1</sup>, Abeer Moanna<sup>2</sup>, Jonathan Colasanti<sup>1</sup>, Valeria D. Cantos Lucio<sup>1</sup>, Wendy S. Armstrong<sup>1</sup>, Anandi N. Sheth<sup>1</sup>, Igbo Ofotokun<sup>1</sup>, Colleen F. Kelley<sup>1</sup>, Vincent Marconi<sup>2</sup>, Cecile D. Lahiri<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Atlanta VA Medical Center, Decatur, GA, USA, <sup>3</sup>Grady Health System, Atlanta, GA, USA

**Background:** The contributions of non-AIDS comorbidities and HIV-related factors to coronavirus disease 2019 (COVID-19) outcomes among persons with HIV (PWH) remain unclear. We aimed to identify risk factors for COVID-19 hospitalization among PWH.

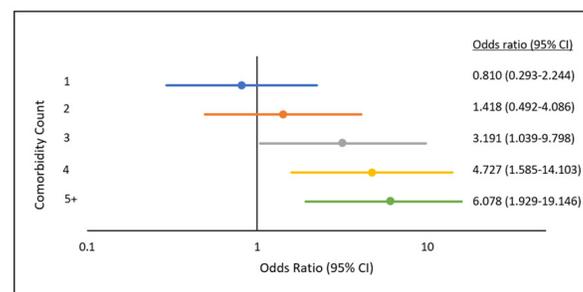
**Methods:** We evaluated all adult (≥18 years) PWH with a positive SARS-CoV-2 PCR evaluated in a public safety-net hospital system, a Ryan White-funded HIV clinic and a Veterans Affairs medical center in Atlanta, GA between March 1, 2020 and November 15, 2020. Demographic and clinical characteristics and COVID-19 disease outcomes were ascertained by medical record abstraction. We performed multivariable logistic regression to determine associations with COVID-19 hospitalization.

**Results:** 180 patients (mean age 49 years, 78% male, 78% Black, 14% Latinx) were included. 97% were on antiretroviral therapy (ART), 91% had HIV-1 RNA <200 copies/mL, and mean CD4 count was 527 cells/mm<sup>3</sup>. 60 patients (33%) were hospitalized, 28 (47%) required supplemental oxygen. Overall mortality rate among PWH was 1.63%; mortality among hospitalized PWH was 5%. 130 patients (72%) had at least 1 non-AIDS comorbidity; 22% had >4 comorbidities (hypertension, dyslipidemia, obesity and diabetes were most prevalent). In univariable models, age, hypertension, dyslipidemia, diabetes, heart disease, and chronic kidney disease were associated with hospitalization. HIV characteristics including CD4 count, viral load, and ART use were not associated with hospitalization. After adjusting for those baseline characteristics

associated with hospitalization, only age [aOR(95%CI) 1.073 (1.036-1.110),  $p<0.0001$ ] and diabetes mellitus [aOR(95%CI) 2.653 (1.027-6.853),  $p=0.0439$ ] were associated with hospitalization. In a multivariable model adjusting only for age, comorbidity count was associated with a 25% increased risk for hospitalization [aOR(95% CI) 1.245 (1.013-1.531),  $p=0.0375$ ]; and having ≥4 comorbidities was associated with a 2.8-fold increased risk of hospitalization compared with 0-1 comorbidities [aOR(95% CI) 2.848 (1.174-6.910),  $p=0.0240$ ] (Figure). In age-adjusted analyses restricted to CD4 <200 cells/mm<sup>3</sup> or HIV-1 RNA >200 copies/mL, HIV-related factors were not associated with hospitalization.

**Conclusion:** In a cohort of PWH with well-controlled HIV and COVID-19, age and non-AIDS comorbidities, but not HIV-related factors, were associated with hospitalization for COVID-19. Further research into causes of severe COVID-19 among PWH is warranted.

**Figure.** The association of comorbidity count and risk of COVID-19 hospitalization among persons with HIV (PWH).



548

## CHARACTERIZING COVID-19 PRESENTATION AND CLINICAL OUTCOMES IN HIV PATIENTS IN THE US

**George A. Yendewa**<sup>1</sup>, Jaime A. Perez<sup>2</sup>, Kayla A. Schlick<sup>2</sup>, Heather A. Tribut<sup>2</sup>, Grace A. McComsey<sup>1</sup>

<sup>1</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>2</sup>University Hospitals Cleveland Medical Center, Cleveland, OH, USA

**Background:** HIV infection is considered a risk factor for severe SARS-CoV-2 (COVID-19) infection; however, there are limited studies assessing the impact of HIV on COVID-19 presentation and clinical outcomes.

**Methods:** We used TriNetX (a large global health research network) to compare adult HIV and non-HIV patients with confirmed SARS-CoV-2 infection who sought care across 44 healthcare facilities in the US January to December 2020. We assessed demographic characteristics, comorbidities, presenting symptoms, laboratory parameters, rate of hospitalization, rate of intensive care service utilization requiring mechanical ventilation and mortality at 30 days after diagnosis. Continuous data were compared using independent t-tests and categorical data were compared using Chi-square or Fishers exact test, as appropriate. Potential confounders were addressed using 1:1 greedy nearest-neighbor propensity score matching based on demographics and key comorbidities. For outcomes of interest, we calculated odds ratios (OR) and 95% confidence intervals (CI), with  $p < 0.05$  considered statistically significant in all analyses.

**Results:** Of 297194 confirmed COVID-19 cases, 1638 (0.6%) were HIV-infected, with > 83% on antiretroviral therapy (ART) and 48% virally suppressed (HIV-1 RNA < 20 copies/μL). Compared with their non-HIV counterparts, HIV patients were more commonly younger ( $p < 0.001$ ), male ( $p < 0.001$ ), African American or Hispanic ( $p < 0.001$ ), had more cardiovascular disease ( $p < 0.001$ ) and other comorbidities, were more symptomatic at presentation and had higher utilization of all healthcare services (Table 1). On laboratory parameters, HIV patients were more anemic ( $p < 0.001$ ), thrombocytopenic ( $p < 0.001$ ) and had elevated serum creatinine ( $p < 0.001$ ), procalcitonin ( $p=0.042$ ) and interleukin-6 ( $p=0.010$ ) levels. In propensity score-matched analysis by demographics and relevant comorbidities, HIV patients had significantly higher odds of hospitalization [OR 1.26, 95% CI (1.04-1.53);  $p=0.023$ ] and severe illness requiring intensive care stay and mechanical ventilation [OR 1.32, 95% CI (1.10-1.58);  $p=0.003$ ]. Mortality at 30 days was higher among HIV patients but did not attain statistical significance (2.9% vs 2.3%;  $p=0.123$ ).

**Conclusion:** In one of the largest studies to date, HIV patients had more underlying risk factors, symptom severity and higher odds of hospitalization

and mechanical ventilation but were not significantly more at risk of death at 30 days after COVID-19 diagnosis compared to non-HIV controls.

Table 1. Comparison of demographic characteristics, comorbidities, presenting symptoms, laboratory parameters and clinical outcomes among HIV and non-HIV COVID-19 patients.

| Characteristics                           | HIV<br>(N=1638) | Non-HIV<br>(N=295556) | p-value |
|---|-----------------|-----------------------|---------|
| Age, years (mean ± SD)                    | 43.34 ± 13.59   | 46.48 ± 18.7          | < 0.001 |
| Male                                      | 1137 (69.4%)    | 130866 (44.3%)        | < 0.001 |
| African American or Hispanic              | 1102 (67.3%)    | 100133 (33.97%)       | < 0.001 |
| Cardiovascular disease                    | 767 (46.8%)     | 77178 (26.1%)         | < 0.001 |
| Obesity                                   | 404 (24.7%)     | 43883 (14.8%)         | < 0.001 |
| Cough                                     | 297 (19.2%)     | 45470 (16.9%)         | 0.0159  |
| Fever                                     | 184 (11.9%)     | 24887 (9.3%)          | 0.0003  |
| Hemoglobin, g/dL (mean ± SD)              | 12.6 ± 2.6      | 12.9 ± 2.2            | 0.0006  |
| Procalcitonin, ng/mL (mean ± SD)          | 2.5 ± 10.1      | 1.3 ± 5.9             | 0.042   |
| Interleukin-6, pg/mL (mean ± SD)          | 258 ± 642       | 98 ± 249              | 0.010   |
| Intensive care and mechanical ventilation | 40 (2.4%)       | 4624 (1.6%)           | 0.005   |
| Mortality at 30 days                      | 47 (2.9%)       | 6708 (2.3%)           | 0.123   |

SD, standard deviation

549 **PREVALENCE AND FACTORS ASSOCIATED WITH SARS-CoV-2 ANTIBODIES IN A SPANISH HIV COHORT**



**Juan Berenguer<sup>1</sup>**, Cristina Díez<sup>1</sup>, María Martín-Vicente<sup>2</sup>, Rafael Mican<sup>3</sup>, María Jesús Pérez-Eliás<sup>4</sup>, Lucio Jesús F. García-Fraile<sup>5</sup>, Francesc Vidal<sup>6</sup>, Inés Suárez-García<sup>7</sup>, Daniel Podzamczar<sup>8</sup>, Juan C. López<sup>1</sup>, Jose R. Arribas<sup>3</sup>, Santiago Moreno<sup>4</sup>, Juan González-García<sup>3</sup>, Salvador Resino<sup>2</sup>, Inmaculada Jarrín<sup>9</sup>

<sup>1</sup>Hospital General Universitario Gregorio Marañón, Madrid, Spain, <sup>2</sup>Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain, <sup>3</sup>La Paz University Hospital, Madrid, Spain, <sup>4</sup>Hospital Ramón y Cajal, Madrid, Spain, <sup>5</sup>Hospital Universitario de La Princesa, Madrid, Spain, <sup>6</sup>Hospital Universitario de Tarragona Joan XXIII, Tarragona, Spain, <sup>7</sup>Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain, <sup>8</sup>Hospital Universitario de Bellvitge, Barcelona, Spain, <sup>9</sup>Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain

**Background:** Within a prospective cohort of people with HIV (PWH) in Spain, we assessed the prevalence of SARS-CoV-2 antibodies (Ab), the proportion of asymptomatic COVID-19, and identified predictors of infection.

**Methods:** We determined SARS-CoV-2 Ab in plasma samples collected from April 1st to September 30th, 2020, from enrollees in the Spanish HIV Research Network Cohort (CoRIS), a prospective national cohort of PWH, naive to ART at study entry, seen for the first time from January 1st, 2004. Samples were stored at -80°C in the Spanish HIV BioBank, and serology was performed using the Platelia SARS-CoV-2 Total Ab assays (BioRad, Hercules, CA, USA). Illness severity (NIH criteria) was assessed by medical records review and, if needed, participant interviews. Multivariable logistic regression analysis was used to identify predictors of seropositivity among the following variables: sex, age, country of birth, education level, comorbidities (hypertension, chronic heart disease, diabetes, non-AIDS related cancer, chronic kidney disease, cirrhosis), route of HIV acquisition, prior AIDS, CD4+ cell count, HIV viral load, and N(t)RTI backbone.

**Results:** During the study period, blood samples were collected and stored in the HIV BioBank from 1,076 consecutive PWH in CoRIS: 88.0% male at birth, median age 43 yr., 72.3% MSM, 97.7% on ART, median CD4+ 688 cells/mm<sup>3</sup>, 91.4% undetectable HIV viral load. SARS-CoV-2 Ab were detected in 91 PWH, for a seroprevalence of 8.5% (95%CI: 6.9% - 10.3%). A total of 41 PWH (45.0%) had asymptomatic infections; the disease was mild in 43 (47.3%), moderate in 4 (4.4%), severe in 3 (3.3%), and 0 critical. Seven PWH (7.7%) were hospitalized. COVID-19 was confirmed by RT-PCR in 22 (24.2%) PWH. Variables independently associated with SARS-CoV-2 seropositivity were birth in Latin American (LA) Countries vs. Spain (adjusted odds ratio [aOR]: 2.34, 95%CI: 1.42 - 3.85; P=.001); arterial hypertension (aOR: 1.63, 95%CI: 1.00 - 2.67; P=.050); and therapy with tenofovir disoproxil fumarate plus emtricitabine (TDF/FTC) vs tenofovir alafenamide (TAF)/FTC as the N(t)RTI backbone (aOR: 0.32, 95%CI: 0.12 - 0.84; P=.021). (Table).

**Conclusion:** A large proportion of SARS-CoV-2 infections among PWH were asymptomatic. Birth in LA- countries and arterial hypertension were associated with increased risk of SARS-CoV-2 seropositivity. Our analysis, adjusted by comorbidities and other variables, suggest that TDF/FTC may prevent SARS-CoV-2 infection among PWH.

Table. Variables independently associated with COVID-19 seropositivity (Ab+) among 1,076 PWH

|                                  | Ab/Total (%)  | Crude OR (95% CI)  | P    | Adjusted OR (95% CI) † | P    |
|----------------------------------|---------------|--------------------|------|------------------------|------|
| <b>Country of birth</b>          |               |                    |      |                        |      |
| Spain                            | 54/753 (7.2)  | Ref                |      | Ref                    |      |
| Latin American Countries         | 33/231 (14.3) | 2.16 (1.36 - 3.42) | .001 | 2.34 (1.42 - 3.85)     | .001 |
| Other                            | 4/91 (4.4)    | 0.60 (0.21 - 1.68) | .328 | 0.64 (0.22 - 1.88)     | .419 |
| <b>Hypertension</b>              |               |                    |      |                        |      |
| No                               | 56/748 (7.5)  | Ref                |      | Ref                    |      |
| Yes                              | 35/328 (10.7) | 1.48 (0.95 - 2.30) | .086 | 1.63 (1.00 - 2.67)     | .050 |
| <b>ART (nrti backbone)</b>       |               |                    |      |                        |      |
| TAF/FTC                          | 40/416 (9.6)  | Ref                |      | Ref                    |      |
| TDF/FTC                          | 5/154 (3.2)   | 0.32 (0.12 - 0.81) | .017 | 0.32 (0.12 - 0.84)     | .021 |
| ABC/3TC                          | 23/279 (8.2)  | 0.84 (0.49 - 1.44) | .537 | 0.86 (0.49 - 1.50)     | .588 |
| Other                            | 17/188 (9.0)  | 0.93 (0.52 - 1.70) | .824 | 0.87 (0.46 - 1.63)     | .667 |
| <b>No antiretroviral therapy</b> | 3/25 (12.0)   | 1.28 (0.37 - 4.47) | .697 | 1.41 (0.37 - 5.39)     | .620 |

† Adjusted by sex at birth, age, mechanism of HIV acquisition, level of education, other comorbidities (chronic heart disease, diabetes, non-AIDS related cancer, chronic kidney disease, cirrhosis), prior AIDS-defining conditions, last CD4+ cell count, and last HIV-RNA detectability.

550 **MYOCARDIAL INJURY AS A PREDICTOR OF MORTALITY AND ADVERSE OUTCOMES IN COVID-19**

**Gavin Manmathan<sup>1</sup>**, Debbie Falconer<sup>1</sup>, Zakee Abdi<sup>1</sup>, Samuel Conway<sup>1</sup>, Athanasios Kosovitsas<sup>1</sup>, Alan Hunter<sup>1</sup>, Callum Little<sup>2</sup>, Sabine Kinloch-de Loes<sup>1</sup>, Colette Smith<sup>2</sup>, Margate A. Johnson<sup>1</sup>, Roby D. Rakhit<sup>2</sup>

<sup>1</sup>Royal Free Hospital, London, UK, <sup>2</sup>University College London, London, UK

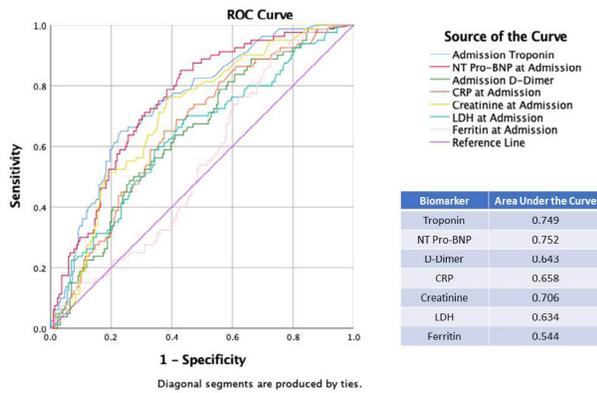
**Background:** The American College of Cardiology suggested physicians should only measure troponin and brain natriuretic peptide (BNP) if myocardial infarction or heart failure were suspected in people with COVID-19. We aimed to evaluate the use of biomarkers on admission to hospital and the impact on mortality and morbidity.

**Methods:** Consecutive patients presenting with COVID-19(reverse transcription PCR positive) between Feb27-May20 2020 were included in this retrospective, observational, single-center study. Clinical information was collected on admission and during hospitalization by physicians and later analysed by specialist cardiology registrars. 1675 patients were PCR +ve with 1036 having a high sensitivity troponin T(hsTropT) on admission. 371(35.8%) patients were hs TropT negative(<15ng/L) and 664(64.1%) had evidence of myocardial injury on admission(hsTropT ≥15ng/L). Subsequently demographic details were compared, as well as primary outcomes of death, ICU admission and COVID severity. Secondary outcomes were ARDS, myocardial infarction (MI); comparison with other biomarkers: NT-proBNP, d-dimer, CRP,LDH and ferritin.

**Results:** Demographic data revealed no significant increase in proportions of Black, Asian or ethnic minorities in the myocardial injury group, however, patients were older(74.9±13.5 v 54.7±13.7yrs; p <0.001) and had significantly more co-morbidities such as diabetes(37 v 13%), hypertension(34 v 29%), ischemic heart disease(16 v 2%), other cardiac conditions(59 v 5%), malignancy(11 v 1%), COPD(9 v 4%), CKD stage ≤3 (40 v 3%) (p <0.01). Mortality was significantly higher in the myocardial injury group, 302(45.5%) v 29(7.8%) p <0.001, as were secondary outcomes of critical COVID (47 v 19%; p<0.001), ARDS (20 v 4%;p<0.001), Type 1 MI (1.6 v 0.01%; p<0.01) and Type 2 MI (44 v 26%; p<0.001). Interestingly, ICU admission (19 v 23%;p=0.09), pulmonary embolism (11 v 6%;p=0.22), stroke (1.1 v 0.5%;p=0.05) did not reach significance. Analysis of bio-markers on admission (Fig 1.) demonstrated hs Trop T (AUC 0.75 CI 0.69-0.81) and NT-pro BNP (AUC 0.75 CI 0.69-0.81) had more sensitivity 83%;85% and specificity 52%;58%, respectively at predicting death than d-dimer, CRP, LDH and ferritin.

**Conclusion:** Early detection of elevated hsTropT and NT-proBNP predicts mortality and morbidity in patient with COVID-19. Routine measurement of cardiac biomarkers should be considered in patients with COVID-19 at the time of hospital admission in order to optimise risk stratification and guide monitoring.

Figure 1. ROC curve analysis of admission biomarkers against death.



## 551 HIGH RATE OF PERSISTENT SYMPTOM 4 MONTHS AFTER COMMUNITY-MANAGED COVID-19 INFECTION

David Darley<sup>1</sup>, Greg Dore<sup>1</sup>, Lucette A. Cysique<sup>1</sup>, Jeff Masters<sup>1</sup>, Anthony Byrne<sup>1</sup>, Bruce Brew<sup>1</sup>, Philip Cunningham<sup>1</sup>, Anthony Kelleher<sup>1</sup>, Gail Matthews<sup>1</sup>, for the ADAPT Study Group

<sup>1</sup>St Vincent's Hospital, Sydney, Australia

**Background:** The spectrum of recovery following community-managed and hospitalized SARS-CoV-2 infection remains uncertain. The aim of the ADAPT study was to determine prevalence and nature of persistent symptoms after community and hospitalised SARS-CoV-2 infection; and to evaluate lung function; health-related quality of life (HRQOL); and neurocognitive abnormalities.

**Methods:** A prospective observational cohort study was performed at St Vincent's Hospital Sydney Australia. Adult patients with a positive SARS-CoV-2 RNA PCR test between Mar-2020 and Apr-2020 including mild, moderate, and severe acute infection were offered enrollment. The clinical outcomes included symptom prevalence at initial infection and follow-up, HRQOL measures, pulmonary function, neurocognition and COVID-19 antibody responses. Initial study assessments were performed up to 4 months after first detection of SARS-CoV-2.

**Results:** Ninety-six patients were recruited following community-managed mild (39%) and moderate (50%), and hospitalized severe (11%) COVID-19 infection. 39.7% patients had persistent symptoms at median 72 days after diagnosis (IQR 65-87), including those in severe (77.8%), moderate (33.3%), and mild (36.7%) sub-populations. The most common persistent symptoms were fatigue (28%), shortness of breath (25%) and cough (21%). Total lung capacity (TLC) was significantly lower after severe, compared with community-managed, COVID-19,  $p=0.05$ . Abnormal diffusion capacity for carbon monoxide values were observed in 16% patients unrelated to acute illness severity. Twenty-four percent patients demonstrated anxiety/depression, as measured by SPHERE-34 item, with the highest proportion in the moderate sub-population (37%). Neurocognitive impairment was low (9%) but associated with abnormal olfaction ( $p=0.02$ ). A high proportion of patients (77-85%) demonstrated positive antibody responses, on four commercial assays, at follow-up and titres were related to acute illness severity.

**Conclusion:** A considerable proportion of patients experience persistent symptoms at 4 months after SARS-CoV-2 infection including one third of community managed patients. High rates of depression and anxiety were reported across the cohort. Outpatient follow-up to further assess those with persistent symptoms after COVID-19 is important to allow multi-disciplinary input, further investigation, and appropriate management. Data collection on the prevalence of persisting symptoms at 8 month follow-up of the ADAPT study is currently underway.

## 552 COGNITIVE DEFICITS ARE NOT A BYPRODUCT OF ANXIO-DEPRESSIVE SYMPTOMS IN COVID-19

Lucette A. Cysique<sup>1</sup>, Yasmin Allen-Davidian<sup>2</sup>, David Darley<sup>1</sup>, Anthony Byrne<sup>3</sup>, Kay Wilhelm<sup>1</sup>, Greg Dore<sup>4</sup>, Gail Matthews<sup>4</sup>, Bruce Brew<sup>3</sup>

<sup>1</sup>University of New South Wales, Sydney, Australia, <sup>2</sup>Macquarie University, North Ryde, Australia, <sup>3</sup>St. Vincent's Hospital, Sydney, Australia, <sup>4</sup>Kirby Institute, Sydney, Australia

**Background:** Cognitive deficits and anxio-depressive symptoms have been described in the recovery phase of COVID-19. Their association, or lack thereof, may assist in better understanding the long-term consequences of COVID-19. **Methods:** Patients underwent neurocognitive and mental health assessment at 2 months after initial SARS-CoV-2 infection as part of the St Vincent's Hospital ADAPT study, a prospective cohort study after COVID-19 disease. Cognition was assessed with the culture fair computerized Cogstate battery. A demographically-corrected composite z-score was created representing global cognitive performance, and then classified as impaired, borderline, and unimpaired. Anxio-depressive symptoms were assessed with the Depression in the Medical Ill scale-10 (DMI-10), the Somatic and Psychological Health Report-34 (SPHERE) Psych subscale, and the Impact of Events Scale-Revised (IESR). The scales scores were amenable to a single Principal Component explaining 80% of the variance. Female sex ( $p<.01$ ) and Non-English-Speaking Background-NESB ( $p=.02$ ) were associated with greater anxio-depressive symptoms but not age, education. Regression analyses tested sex and NESB unadjusted and adjusted predictions of anxio-depression to cognition.

**Results:** 132 patients (mean age=46±15; 40% women, median education=16 years, 10% NESB) were tested after predominantly community-managed COVID-19 (10% hospitalised). 17% had impaired global cognition, and 10% had borderline deficit. 25% had elevated symptoms on the DMI-10 (score>9), 13% on the IESR (score>24) and 35% on the SPHERE Psych scale (score≥2). Anxio-depression was not predictive of cognitive performance (unadjusted  $p=.43$ ; adjusted  $p=.98$ ) and of impaired/unimpaired status (unadjusted  $p=.50$ ; adjusted  $p=.78$ ). Anxio-depression tended to predict of borderline (vs. unimpaired) performance in unadjusted ( $p=.08$ ) and adjusted ( $p=.09$ ) analyses. This was explained by the fact that women who had borderline performance tended to report higher anxio-depressive symptoms compared to their peers who were unimpaired ( $p<.06$ ); further impaired women (vs. unimpaired) tended to report the least anxio-depressive symptoms ( $p=.09$ ).

**Conclusion:** Cognitive deficits are not a by-product of anxio-depressive symptoms in recovering COVID-19 patients. Women appear to have a higher degree of introspection and reaction to very mild cognitive decline. Cognitive changes appear to be a direct consequence of COVID-19.

## 553 EVALUATING FACTORS MEDIATING THE RELATIONSHIP BETWEEN MALE SEX AND COVID-19 SEVERITY

Randy Stalter<sup>1</sup>, Vidya Atluri<sup>1</sup>, Fan Xia<sup>2</sup>, Katherine K. Thomas<sup>1</sup>, Kristine Lan<sup>1</sup>, Alex Greninger<sup>1</sup>, Rena Patel<sup>1</sup>

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>National Alzheimer's Coordinating Center, Seattle, WA

**Background:** Males have experienced higher rates of severe COVID-19 outcomes compared to females but the underlying causal mechanisms of this relationship are not well understood. We leveraged existing electronic medical records (EMR) to evaluate associations between sex and COVID-19 test positivity, disease severity, viral burden, and death, and assess factors that mediate the relationship between male sex and severe COVID-19 disease.

**Methods:** We conducted a retrospective cohort study with data collected from University of Washington Medicine EMR from March 1 to September 29, 2020. All persons, regardless of age, were included if they had a conclusive diagnostic COVID-19 PCR test result. We defined severe COVID-19 disease as a score >5 on the WHO clinical progression scale. We used Poisson regression to assess sex differences in risk for COVID-19 test positivity, disease severity and COVID-19 related death, and linear regression to compare viral cycle threshold at the first positive test. We conducted mediation analyses to assess interventional indirect effects of male sex on severe COVID-19 risk through socioeconomic status (SES, based on area deprivation and insurance type), comorbidities, and inflammation status. Models controlled for age and race/ethnicity.

**Results:** Of individuals with SARS-CoV-2 testing records, 32,919 males and 34,733 females had a conclusive PCR test during our observation period. Males were 13% more likely to test positive than females in multivariable analysis (RR=1.13; 95% CI: 1.04-1.24; Table). Males had 85% higher risk for severe

COVID-19 disease (RR=1.85; 95% CI: 1.33-2.62) and 66% higher risk for COVID-19 related death (RR=1.66; 95% CI: 0.95-2.98) than females following a positive test result. No difference was observed in cycle threshold at first positive test between males and females (p=0.69). Mediation analyses indicated a significant interventional indirect effect of male sex on severe COVID-19 disease through inflammation status (RR=1.07; 95% CI: 1.01-1.13), and less so through SES or comorbidities.

**Conclusion:** In our cohort, males had higher test positivity and greater risk of COVID-19 severity and death. This relationship between male sex and severe COVID-19 seems to act in part through inflammation status. Additional analyses in larger cohorts are needed to better understand the full range of socio-behavioral and biologic factors that mediate the relationship between sex and poor COVID-19 outcomes.

**Table. Assessing sex differences in COVID-19 test positivity, disease severity, death and viral burden**

|  | Males                | Females              | Estimate (95% CI)<br>Reference: Females |
|--|----------------------|----------------------|---|
| Test positivity, n (%)   | 1469/32919<br>(4.5%) | 1372/34733<br>(4.0%) | RR: 1.13 (1.04-1.24)                    |
| Severe COVID-19 disease, n (%) <sup>a</sup>  | 145/1469<br>(9.9%)   | 77/1372<br>(5.6%)    | RR: 1.85 (1.33-2.62)                    |
| COVID-19 related death, n (%) <sup>a</sup>   | 64/1469<br>(4.4%)    | 42/1372<br>(3.1%)    | RR: 1.66 (0.95-2.98)                    |
| SARS-CoV-2 cycle threshold at first positive result, median (IQR) <sup>a</sup>   | 25.2<br>(19.5-32.4)  | 25.9<br>(19.0-33.0)  | Mean difference:<br>-0.006 (-0.03-0.03) |
| <i>Mediation analysis of the relationship between male sex and severe COVID-19 disease<sup>a,b</sup></i>   |                      |                      |   |
| Total causal effect  |                      |                      | RR: 1.89 (1.27-2.61)                    |
| Interventional indirect effect through SES   |                      |                      | RR: 0.98 (0.96-1.01)                    |
| Interventional indirect effect through comorbidities   |                      |                      | RR: 1.00 (1.99-1.02)                    |
| Interventional indirect effect through inflammation status   |                      |                      | RR: 1.07 (1.01-1.13)                    |
| Interventional indirect effect not through SES, comorbidities, or inflammation status  |                      |                      | RR: 1.57 (1.10-2.04)                    |
| <small>RR=relative risk; IQR=interquartile range; CI=confidence interval; SES=socioeconomic status<br/> <sup>a</sup>Among individuals who received a positive COVID-19 PCR result<br/> <sup>b</sup>The mediation analysis uses a subset of the cohort included in the main regression models due to missing data for mediators<br/>                     All models adjusted for age and race/ethnicity<br/>                     Definitions: Severe COVID-19 disease defined as score &gt;5 on WHO clinical progression scale; lower SES defined as living in a location with an area deprivation index score above the national median or having income-based insurance; comorbidities measured using Charlson Comorbidity Index score (possible score range 0-33); inflammation status defined as the number of the following markers above the reference range for healthy adults (possible score range 0-8): interleukin 6 (IL-6), erythrocyte sedimentation rate (ESR), ferritin, high sensitivity C reactive protein (hsCRP), lactate dehydrogenase (LDH), lymphocytes, neutrophils, and white blood cells</small> |                      |                      |   |

**554 LONG-TERM SEQUELA OF SARS-CoV-2 INFECTION IN A RETROSPECTIVE NEW YORK CITY COHORT**

**Sherif Shoucri<sup>1</sup>**, Matthew A. Adan<sup>2</sup>, Lawrence Purpura<sup>1</sup>, Clare DeLaurentis<sup>1</sup>, Deborah Theodore<sup>1</sup>, Michael T. Yin<sup>1</sup>, Magdalena Sobieszczyk<sup>1</sup>, Delivette Castor<sup>1</sup>, Jason Zucker<sup>1</sup>, for the Columbia Longitudinal COVID Group  
<sup>1</sup>Columbia University Medical Center, New York, NY, USA, <sup>2</sup>Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

**Background:** The long-term sequelae of coronavirus disease 2019 (COVID-19) have been increasingly recognized. Cardiac, pulmonary, and neuropsychiatric symptoms have been reported to persist up to two months after hospitalization. However, much remains to be learned about the durable long-term effects of COVID-19 for patients and the health care system. Here, we describe the persistence of COVID-19 sequelae up to six months after presentation.

**Methods:** We examined the electronic medical records of the first 1190 patients diagnosed with SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction assay and hospitalized at a quaternary-care center in New York City. All initial hospital presentations occurred between March 1 and April 8, 2020. We manually abstracted data for two follow-up periods representing three- and six-months post-hospitalization. Abstracted information included type and dates of encounters; use of tele-health; presence and persistence of symptoms; morbidity; and mortality. Descriptive statistics for categorical and continuous variables were tabulated and distributions were examined by visit; at presentation, three months and six months.

**Results:** Patients had a median age of 60 and 61 years at three and six months, respectively. About 45% were female and 50% identified as Hispanic/Latinx. Of 1190 patients, 78% (N=928) survived their initial hospitalization. Among the 61% (n=570) of survivors who had follow-up encounters at three and six months, patients frequently reported cardiopulmonary symptoms (35.7% and 28%), dyspnea (22.1% and 15.9%), generalized symptoms (25.4% and 26.4%) and neuropsychiatric symptoms (20.1% and 24.2%). Tele-health encounters represented 59% and 28.2% of encounters at three and six-months, respectively. Twenty-percent of patients had reduced mobility or reduced independence in the six months after hospitalization. Of survivors, 17% were

discharged to a nursing or rehabilitation facility and 10.3% remained there at three months post-hospitalization.

**Conclusion:** The prevalence was high of at least one COVID-associated symptom six months after hospitalization. Cardiopulmonary symptoms were most common and persisted longer than previously reported. Providers, patients, and their families must be sensitized to and anticipate these potential sequelae. Further follow-up and studies of COVID-19 survivors are necessary to confirm these findings and investigate outcomes beyond six months.

**Table 1** Persistent symptoms<sup>1</sup> reported for patients with follow-up encounters

| Characteristic                   | Initial Hospitalization<br>N = 570 (%) | 3 months<br>N = 488 (%) | 6 months<br>N = 364 (%) | 3 and 6 months<br>N = 282 (%) |
|----------------------------------|--|-------------------------|-------------------------|-------------------------------|
| <b>Cardiopulmonary Symptoms</b>  | 496 (87.0%)                            | 174 (35.7%)             | 102 (28.0%)             | 37 (13.1%)                    |
| Dyspnea                          | 354 (62.1%)                            | 108 (22.1%)             | 58 (15.9%)              | 28 (9.9%)                     |
| Cough                            | 430 (75.4%)                            | 78 (16.0%)              | 37 (10.2%)              | 8 (2.8%)                      |
| Chest Pain                       | 74 (13.0%)                             | 37 (7.6%)               | 30 (8.2%)               | 3 (1.1%)                      |
| Lower Extremity Edema            | 4 (0.7%)                               | 25 (5.1%)               | 22 (6.0%)               | 6 (2.1%)                      |
| <b>Generalized Symptoms</b>      | 468 (82.1%)                            | 124 (25.4%)             | 96 (26.4%)              | 27 (9.6%)                     |
| Fever                            | 441 (77.4%)                            | 42 (8.6%)               | 13 (3.6%)               | 3 (1.1%)                      |
| Fatigue                          | 31 (5.4%)                              | 44 (9.0%)               | 38 (10.4%)              | 7 (2.5%)                      |
| Myalgias or Arthralgias          | 164 (28.8%)                            | 54 (11.1%)              | 64 (17.6%)              | 18 (6.4%)                     |
| Anosmia or Agnosia               | 21 (3.7%)                              | 5 (1.0%)                | 3 (0.8%)                | 0 (0%)                        |
| <b>Neuropsychiatric Symptoms</b> | 112 (19.6%)                            | 98 (20.1%)              | 88 (24.2%)              | 21 (7.4%)                     |
| Weakness                         | 21 (3.7%)                              | 41 (8.4%)               | 34 (9.3%)               | 11 (3.9%)                     |
| Altered Mentation                | 32 (5.6%)                              | 28 (5.7%)               | 20 (5.5%)               | 4 (1.4%)                      |
| Headache                         | 62 (10.9%)                             | 26 (5.3%)               | 21 (5.8%)               | 2 (0.7%)                      |
| Depression or Anxiety            | 0 (0%)                                 | 17 (3.5%)               | 18 (4.9%)               | 3 (1.1%)                      |
| Gait Instability                 | 1 (0.2%)                               | 9 (1.8%)                | 18 (4.9%)               | 3 (1.1%)                      |
| <b>Gastrointestinal Symptoms</b> | 239 (41.9%)                            | 80 (16.4%)              | 75 (20.6%)              | 13 (4.6%)                     |
| Nausea or Vomiting               | 124 (21.8%)                            | 26 (5.3%)               | 23 (6.3%)               | 1 (0.4%)                      |
| Abdominal Pain                   | 39 (6.8%)                              | 25 (5.1%)               | 34 (9.3%)               | 4 (1.4%)                      |
| Diarrhea                         | 154 (27.0%)                            | 18 (3.7%)               | 12 (3.3%)               | 1 (0.4%)                      |

<sup>1</sup> Persistent symptoms = symptoms that did not resolve during each three-month follow-up period

**555**

**SARS-CoV-2 RNA LEVELS CORRELATE WITH SYMPTOM DURATION BUT NOT SEVERITY IN OUTPATIENTS**

**Kara W. Chew<sup>1</sup>**, Carlee B. Moser<sup>2</sup>, Jonathan Li<sup>3</sup>, Robert Coombs<sup>4</sup>, Eric S. Daar<sup>1</sup>, David A. Wohl<sup>5</sup>, Evgenia Aga<sup>2</sup>, Justin Ritz<sup>2</sup>, Arzhang Cyrus Javan<sup>6</sup>, Joseph J. Eron<sup>5</sup>, Judith S. Currier<sup>1</sup>, Michael Hughes<sup>2</sup>, Davey M. Smith<sup>7</sup>, for the ACTIV-2/A5401 Study Team

<sup>1</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>4</sup>University of Washington, Seattle, WA, USA, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>National Institutes of Health, Rockville, MD, USA, <sup>7</sup>University of California San Diego, La Jolla, CA, USA

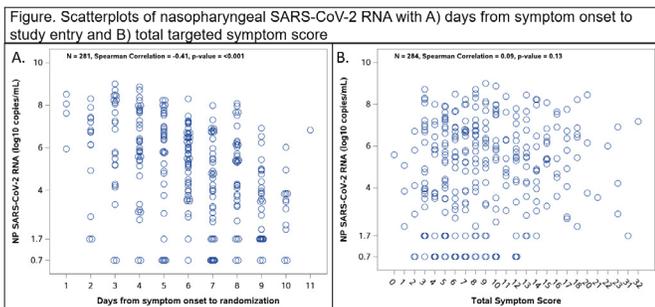
**Background:** The relationship between nasopharyngeal (NP) SARS-CoV-2 RNA, demographics and symptom characteristics in non-hospitalized persons with COVID-19 is not well described.

**Methods:** ACTIV-2 is a phase 2/3 adaptive platform trial testing antivirals for SARS-CoV-2 in symptomatic non-hospitalized adults. We analyzed associations between NP quantitative SARS-CoV-2 RNA (Abbott m2000sp/rt) and COVID-19 symptomatology in 284 participants with both a NP swab and symptom diary prior to study intervention. The diary included 13 targeted symptoms and questions about overall severity of COVID-19 symptoms, each scored as none, mild, moderate, or severe (and very severe for overall severity) and general physical health (scored as poor, fair, good, very good, excellent). Wilcoxon tests were used to compare NP RNA levels between pre-defined groups. Spearman correlations, Jonckheere-Terpstra trend tests, and linear regressions evaluated associations between symptom measures and NP RNA.

**Results:** Participants were 49% female, 82% white, 9% black, and 27% Latinx. Median age was 46 years and 50% met the protocol definition of higher risk for COVID-19 progression (age ≥55 years and/or protocol-defined comorbidities); 32% reported moderate and 5% severe symptoms. Median (Q1, Q3) time from onset of symptoms to NP swab/symptom assessment was 6 (4, 8) days. NP RNA was above the lower limit of quantification in 85%; median (Q1, Q3) was 5.4 (3.5, 6.8) log<sub>10</sub> copies/mL. Higher RNA levels were associated with shorter symptom duration (median 6.5 vs 4.7 log<sub>10</sub> copies/mL for ≤5 vs >5 days) but not total symptom score (Figure). Controlling for symptom duration, higher NP RNA levels were associated with better general physical health (p=0.02) and more severe body/muscle pain (p=0.04). No associations were observed with symptom severity (sum of scores or overall severity) or any other symptoms. There was no association between NP RNA and age or risk category for COVID-19 progression.

**Conclusion:** In symptomatic outpatients, NP SARS-CoV-2 RNA levels were higher in persons with more recent symptom onset, but were not associated

with symptom severity or risk for disease progression. The range of viral RNA shedding was remarkably similar across the range of symptom severity, suggesting symptom severity may not correlate with transmission risk or the potential to respond to antiviral therapy. Outpatient trials aimed at evaluating antiviral activity of new agents should focus enrollment on participants with recent onset of symptoms.



## 556 ROUTINIZATION OF TB INFECTION SCREENING WITH CD4 AND VIRAL LOAD MONITORING IN BRAZIL

**Leila H. Chaisson**<sup>1</sup>, Paula Travassos<sup>2</sup>, Silvia Cohn<sup>3</sup>, Solange Cavalcante<sup>4</sup>, Valeria Saraceni<sup>2</sup>, Renata Spener-Gomes<sup>5</sup>, Leda F. Jamal<sup>6</sup>, Ana P. Loch<sup>6</sup>, Jose V. Madruga<sup>6</sup>, Marcelo Cordeiro-Santos<sup>5</sup>, Jonathan Golub<sup>3</sup>, Betina Durovni<sup>2</sup>, for the PREVINE-TB Research Group

<sup>1</sup>University of Illinois at Chicago, Chicago, IL, USA, <sup>2</sup>Secretaria Municipal de Saúde do Rio de Janeiro, Rio de Janeiro, Brazil, <sup>3</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>4</sup>Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil, <sup>5</sup>Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, Brazil, <sup>6</sup>Centro de Referência e Treinamento DST/AIDS-SP, Sao Paulo, Brazil

**Background:** In Brazil, annual screening for latent tuberculosis infection (LTBI) via tuberculin skin testing (TST) is recommended for people with HIV (PWH) with CD4>350 cells/ $\mu$ L to guide tuberculosis preventive therapy (TPT). However, screening remains infrequent and TPT is markedly underutilized. We hypothesized that a strategy pairing screening via interferon-gamma release assay (IGRA) with routine CD4 and viral load (VL) monitoring could improve LTBI screening and TPT uptake for PWH.

**Methods:** PREVINE-TB is a multi-center study in four clinics in Rio de Janeiro, Manaus, and São Paulo, Brazil, with the overall objective of improving LTBI evaluation and TPT uptake for PWH. We implemented a strategy to integrate IGRA testing (via QuantiferON-TB Gold Plus, QFT+) at routine CD4/VL blood draws. We enrolled PWH presenting for routine clinic or laboratory visits who were eligible for LTBI evaluation according to Brazilian national guidelines (CD4>350 or CD4 unknown; no negative TST within 12 months; no history of a positive TST, TPT, or TB treatment). Clinicians were trained to order IGRA, with blood draws scheduled for the patient's next routine CD4 and/or VL test. To assess IGRA uptake during the 6-month PREVINE-TB pilot period, we determined the proportions of patients enrolled, referred for IGRA, and completing IGRA; and LTBI prevalence among those tested.

**Results:** From Jun-Nov 2020, we screened 1,504 PWH with CD4>350 or CD4 unknown and enrolled 665 (44%) eligible for IGRA, including 388 (58%) presenting to the laboratory and 277 (42%) presenting for clinic appointments. Of 839 not enrolled, 421 (50%) were ineligible for IGRA (including 124 who previously received TPT and 263 previously treated for active TB) and 314 (37%) were not referred by clinic physicians. Among 665 enrolled, we excluded 20 (3%) with incomplete data. Among 645 included, median age was 44 years (IQR 35-55) and 168 (26%) were female. IGRA was ordered for 642 (99.5%) and paired with a CD4 and/or VL order for 580/642 (90%). At the time of analysis, 491 (77%) patients had completed IGRA and 151 (23%) were scheduled for testing at a later date. 104/491 (21%) were IGRA-positive, including 59/185 (32%) in Rio de Janeiro, 24/133 (18%) in Manaus, and 20/173 (12%) in São Paulo.

**Conclusion:** Prevalence of LTBI among PWH receiving routine HIV care in three cities in Brazil was high, particularly in Rio de Janeiro. Routinely linking IGRA to CD4 and/or VL may increase known LTBI status, potentially leading to increased TPT.

## 557 ASSESSMENT OF TUBERCULOSIS DISEASE ACTIVITY IN MTB-INFECTED HIV PATIENTS OVER TIME

**Inge Kroidl**<sup>1</sup>, Mohamed I. Ahmed<sup>2</sup>, Sacha Horn<sup>1</sup>, Christina Polyak<sup>3</sup>, Allahna Esber<sup>2</sup>, Ajay Parikh<sup>4</sup>, Leigh A. Eller<sup>4</sup>, Hannah Kibuuka<sup>5</sup>, Jonah Maswai<sup>6</sup>, John Owuoth<sup>6</sup>, Rebecca Loose<sup>1</sup>, Michael Hoelscher<sup>1</sup>, Julie Ake<sup>6</sup>, Christof Geldmacher<sup>1</sup>

<sup>1</sup>University Hospital, LMU Munich, Munich, Germany, <sup>2</sup>LUM Munich, Munich, Germany, <sup>3</sup>US Military HIV Research Program, Silver Spring, MD, USA, <sup>4</sup>U.S. Military HIV Research Program, Silver Spring, MD, USA, <sup>5</sup>Makerere University Walter Reed Project, Kampala, Uganda, <sup>6</sup>U.S. Military HIV Research Program, Munich, Germany

**Background:** HIV infected patients in sub-Saharan Africa are at high risk of developing active tuberculosis (aTB). Studies assessing aTB disease activity and transmissibility over long periods in Mycobacterium tuberculosis (MTB) infected people living with HIV (PLWH) are lacking and difficult to conduct. Previous studies demonstrated that phenotypic characteristics of MTB-specific CD4 T cells – in particular expression of activation and maturation markers – detects aTB with high accuracy.

**Methods:** During the African Cohort Study (AFRICOS) Tuberculosis sub-study, 2024 East African PLWH from Kenya (Kisumu and South Rift Valley) and Uganda (Kayunga,) were subjected to molecular detection of MTB during yearly intervals from 2013 to 2017. Longitudinal PBMC sample sets from 46 patients were selected into three groups matched for age, sex and ART status; patients with clinically latent MTB infection was defined by continuous MTB sputum-negativity and absence of aTB symptoms; aTB patients were sputum MTB+ at baseline and initiated TB treatment. Incipient TB cases were unsuspected for aTB at enrolment and developed sputum MTB+ aTB during the course of the AFRICOS study. In total 242 visits and 1556 person months were analyzed for MTB-specific T cell activation and maturation using intracellular cytokine staining as a surrogate marker of aTB disease activity.

**Results:** CD38 expression on MTB-specific T cells, but not bulk CD4 T cells, specifically differentiated active aTB from LTBI ( $p<0.001$ ) and was reduced upon TB treatment initiation ( $p<0.001$ ). 67% and 23% of incipient TB cases had activated MTB-specific T cells at 6 and 12 months before aTB diagnoses, respectively. Transient flurries of MTB-specific T cell activation were also often observed in the majority of HIV patients with LTBI and after the end of TB treatment. These typically resolved without Isoniazid treatment. However, recurrent aTB was associated with persistent/recurrent MTB-specific T cell activation after the end of treatment.

**Conclusion:** The majority of HIV patients with clinically latent MTB infection experience periods of sub-clinical disease that either are spontaneously controlled or progress to aTB. Subclinical TB disease activation starts between 6 to 12 months prior to the sputum-based diagnoses of aTB in the majority of incipient TB cases. After the end of TB treatment, persistent or recurrent MTB-specific T cell activation is associated with recurrent aTB and/or treatment failure.

|                                      | Total         | Rio de Janeiro | Manaus        | São Paulo     |
|--------------------------------------|---------------|----------------|---------------|---------------|
| PLWH with CD4>350 or CD4 unknown     | 1504          | 522            | 678           | 304           |
| Not eligible for IGRA                | 421 (28%)     | 184 (35%)      | 180 (27%)     | 57 (19%)      |
| TST-negative within 12 months        | 34 (8%)       | 16 (9%)        | 11 (6%)       | 7 (12%)       |
| Prior positive TST                   | 18 (4%)       | 3 (2%)         | 10 (6%)       | 5 (9%)        |
| Prior TPT                            | 124 (29%)     | 57 (31%)       | 49 (27%)      | 18 (32%)      |
| Prior TB treatment                   | 263 (62%)     | 113 (61%)      | 116 (64%)     | 34 (60%)      |
| Active TB symptoms                   | 1 (0.1%)      | 0 (0%)         | 0 (0%)        | 1 (0.3%)      |
| Not referred for IGRA                | 314 (21%)     | 82 (16%)       | 232 (34%)     | 0 (0%)        |
| Patient declined to participate      | 103 (7%)      | 8 (2%)         | 59 (9%)       | 36 (12%)      |
| Enrolled                             | 665 (44%)     | 248 (48%)      | 207 (31%)     | 210 (69%)     |
| IGRA results                         |               |                |               |               |
| IGRA ordered                         | 642           | 243            | 205           | 194           |
| IGRA order paired with CD4 and/or VL | 580 (90%)     | 220 (91%)      | 174 (85%)     | 186 (96%)     |
| IGRA completed                       | 491 (77%)     | 185 (76%)      | 133 (65%)     | 173 (89%)     |
| IGRA positive                        | 104 (21%)     | 59 (32%)       | 24 (18%)      | 21 (12%)      |
| Median CD4 (IQR)                     | 500 (329-738) | 475 (337-733)  | 462 (257-642) | 703 (597-804) |
| VL undetectable                      | 314 (86%)     | 170 (93%)      | 56 (60%)      | 88 (96%)      |

## 558 M. TUBERCULOSIS EXOSOME DETECTION FOR TB DIAGNOSIS IN CHILDREN LIVING WITH HIV

Sylvia LaCourse<sup>1</sup>, Wenshu Zheng<sup>2</sup>, Jaclyn Escudero<sup>1</sup>, Lisa Cranmer<sup>3</sup>, Irene Njuguna<sup>4</sup>, Dalton Wamalwa<sup>5</sup>, Elizabeth Maleche-Obimbo<sup>5</sup>, Christopher Lyon<sup>2</sup>, Grace John-Stewart<sup>1</sup>, Tony Hu<sup>2</sup>

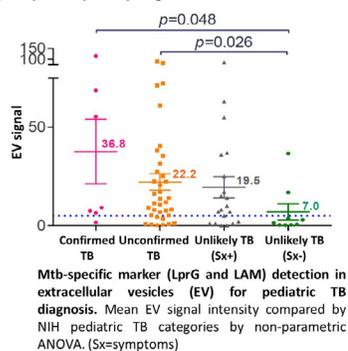
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Tulane University, New Orleans, LA, USA, <sup>3</sup>Emory University, Atlanta, GA, USA, <sup>4</sup>Kenyatta National Hospital, Nairobi, Kenya, <sup>5</sup>University of Nairobi, Nairobi, Kenya

**Background:** Non-sputum-based diagnostics for pediatric TB detection and treatment response are urgently needed for children living with HIV (CLHIV) who have high TB morbidity and mortality and are often missed by respiratory sampling. Exosomes are small extracellular vesicles (EVs) secreted by cells originating from endosomal cell compartments. We developed a nanoplasmon-enhanced scattering (nPES) assay which detects and quantifies *M. tuberculosis*-specific markers (LprG and lipoarabinomannan (LAM) in EVs (Mtb-EVs) using as little as 1  $\mu$ L of plasma.

**Methods:** Cryopreserved plasma from hospitalized children enrolled in a trial (NCT02063880) of urgent (<48 hrs) vs. post-stabilization (7-14 days) ART was evaluated by Mtb-EV nPES assay. Children underwent baseline TB investigations including sputum or gastric aspirates Xpert and culture, and stool Xpert. Plasma was collected at baseline, 2, 4, 12, and 24 weeks when possible. Children were classified per NIH pediatric TB diagnostic criteria as confirmed (Xpert and/or culture positive), unconfirmed (> 2 of: either signs/symptoms suggestive of TB, abnormal CXR, TB exposure or tuberculin skin test positive, or having positive TB treatment response), or unlikely TB.

**Results:** Among 72 children, 60% were male, median age was 1.4 years (IQR 0.6-3.7), 80% were severely immunosuppressed (WHO criteria), and 31% died. Ten percent (7/72) had confirmed, 50% (36/72) unconfirmed, and 40% (29/72) had unlikely TB. Twenty-four initiated TB treatment, with 14 (58%) considered to have treatment response. Mtb-EV nPES sensitivity was 86% (6/7) among confirmed and 72% (26/36) among unconfirmed TB cases. Specificity was 48% (14/29) among unlikely TB cases; but increased to 78% (7/9) among unlikely TB cases without symptoms. Mean Mtb-EV signals were higher among confirmed vs. unlikely TB overall and vs. unlikely TB without symptoms (both  $p < 0.05$ ) and among unconfirmed TB vs. unlikely TB without symptoms ( $p < 0.03$ ) (Figure). Mtb-EV concentration decreased following TB treatment initiation in children with available longitudinal samples among 100% (4/4) CLHIV with confirmed TB and 67% (8/12) of unconfirmed TB cases with clinical improvement.

**Conclusion:** Mtb-EVs detected by nPES is a promising means of TB detection and monitoring of treatment response using non-respiratory sample which requires minimal blood volume in CLHIV. Detectable Mtb-EVs in symptomatic immunocompromised CLHIV without microbiologic confirmation may indicate TB missed by respiratory sampling.



## 559 SERUM MARKERS AND INTEGRATIVE MULTI-OMICS OF TB DIAGNOSIS IN ADVANCED HIV

Sonya Krishnan<sup>1</sup>, Artur T. Queiroz<sup>2</sup>, Amita Gupta<sup>1</sup>, Nikhil Gupte<sup>1</sup>, Gregory P. Bisson<sup>3</sup>, Johnstone Kumwenda<sup>4</sup>, Kogieleum Naidoo<sup>5</sup>, Lerato Mohapi<sup>6</sup>, Vidya Mave<sup>7</sup>, Rosie Mngqibisa<sup>8</sup>, Javier R. Lama<sup>9</sup>, Mina C. Hosseinpour<sup>10</sup>, Bruno B. Andrade<sup>2</sup>, Petros Karakousis<sup>1</sup>, for the ACTG A5274 REMEMBER and NWCs 414 Study Team <sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Instituto Gonçalo Moniz, Salvador, Brazil, <sup>3</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>4</sup>University of Malawi, Blantyre, Malawi, <sup>5</sup>University of KwaZulu-Natal, Durban, South Africa, <sup>6</sup>University of the Witwatersrand, Johannesburg, South Africa, <sup>7</sup>Byramjee Jeejeebhoy Government Medical College, Pune, India, <sup>8</sup>Durban International Clinical Research Site, Durban, South Africa, <sup>9</sup>Asociacion Civil Impacta Salud y Educacion, Barranco, Peru, <sup>10</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

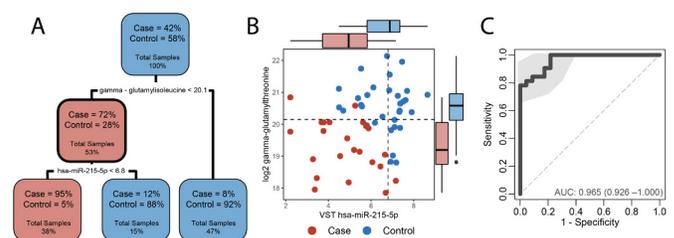
**Background:** Tuberculosis (TB) accounts for a large burden of morbidity and mortality among persons living with HIV (PLWH). Conventional methods of TB diagnosis, including smear microscopy and Xpert MTB/RIF have lower sensitivity in PLWH. Novel high-throughput approaches, such as miRNAomics and metabolomics, may advance our insights into subclinical and difficult to diagnose TB, especially in very advanced HIV.

**Methods:** We conducted a case-control study leveraging REMEMBER, a multi-country, open-label randomized controlled trial comparing 4-drug empiric TB treatment with isoniazid preventive therapy in PLWH initiating ART with CD4 cell counts <50 cells/ $\mu$ L. Active TB was ruled out at baseline. A total of 23 Cases (incident TB within 48 weeks post-ART initiation) were site-matched with up to 2 Controls. We performed miRNA next generation sequencing (QIAGEN), liquid chromatography-mass spectrometry quantitative metabolomic analysis (Metabolon, Inc.), and multiplex immunoassays (Luminex) on serum samples obtained at time of TB diagnosis. Multi-omics data were integrated, and the decision tree algorithm was used to identify the best model for TB diagnosis. The accuracy was measured by receiver operating characteristic (ROC) curve and area under the curve (AUC).

**Results:** The majority of participants were from South Africa and India. The median time to TB diagnosis was 4.6 weeks (IQR 2-16.1), with 12 pulmonary and 11 extrapulmonary cases. Differentially expressed miRNA analysis revealed 11 altered miRNAs, with fold change higher than  $\pm 1.4$  in Cases relative to Controls ( $P < 0.05$ ). Differentially altered metabolite analysis showed no significant alterations in metabolites between Cases and Controls. We found higher TNF $\alpha$  and IP-10/CXCL10 in Cases ( $p = 0.011$ ,  $p = 0.0005$ ), and higher MDC/CCL22 in Controls ( $p = 0.0072$ ). A decision tree algorithm identified gamma-glutamylthreonine and hsa-miR-215-5p as the optimal variables to classify incident TB Cases (AUC 0.965). hsa-miR-215-5p, which targets genes in the TGF- $\beta$  signaling pathway, was downregulated in Cases. Gamma-glutamylthreonine, a breakdown product of protein catabolism, was less abundant in Cases. Integration of cytokine markers did not improve the AUC.

**Conclusion:** Use of a machine learning approach in the multi-omics data from advanced HIV participants revealed two variables with the ability to accurately discriminate TB Cases from Controls.

Figure:



Machine learning results applied in the combined multi-omic data. A – Decision tree from the Case and Control classification. B – Dot plot from variables selected by decision tree with dotted lines the decision thresholds. The boxplots parallel to X-axis shows the hsa-miR-215-5p variance stabilizing transformation (VST) values by group and the boxplots parallel to the Y-axis shows the  $\log_2$  gamma-glutamylthreonine values by groups. Cases are denoted in red and Controls in blue. C – Receiver operating characteristic (ROC) curve from the decision tree variables demonstrating the sensitivity, specificity, and area under the curve (AUC) of hsa-miR-215-5p and gamma-glutamylthreonine to discriminate participants by TB status.

## 560 OUTCOMES OF ISONIAZID PREVENTIVE THERAPY AMONG CHILDREN LIVING WITH HIV IN KENYA

**Dickens O. Onyango**<sup>1</sup>, Courtney M. Yuen<sup>2</sup>, Samuel Gurrion<sup>3</sup>, Jerphason O. Mecha<sup>4</sup>, Daniel Matemo<sup>4</sup>, Elizabeth Oele<sup>1</sup>, John Kinuthia<sup>4</sup>, Grace John-Stewart<sup>5</sup>, Sylvia LaCourse<sup>5</sup>

<sup>1</sup>Kisumu County Department of Health, Kisumu, Kenya, <sup>2</sup>Harvard Medical School, Boston, MA, USA, <sup>3</sup>Kenya Medical Research Institute, Nairobi, Kenya, <sup>4</sup>Kenyatta National Hospital, Nairobi, Kenya, <sup>5</sup>University of Washington, Seattle, WA, USA

**Background:** Tuberculosis (TB) is a leading cause of morbidity and mortality among children living with HIV (CLHIV). Isoniazid (INH) preventive therapy (IPT) is effective in reducing TB incidence among CLHIV. However, there are limited data on the IPT cascade in CLHIV including TB status after 24 months.

**Methods:** We evaluated the IPT cascade among CLHIV newly enrolled in HIV care in eight high-volume HIV clinics in western Kenya. Medical record data was abstracted for CLHIV aged <15 years who were enrolled from September 2015 through July 2019 (with at least 12 months follow up time) using standardized case report forms. We assessed screening for TB symptoms and IPT eligibility, IPT initiation, IPT outcomes at six months, and TB status at 12, 18 and 24 months. TB incidence rate was compared by IPT initiation and completion status. Correlates of IPT non-initiation and non-completion were assessed using age and sex adjusted robust Poisson regression models.

**Results:** Overall, 856 CLHIV were newly enrolled in HIV care, of whom 98% (n=841) underwent screening for TB symptoms and IPT eligibility, 2.5% (n=21) were diagnosed with active TB; 98% (n=820) of screened CLHIV were eligible for IPT. Median age was 5 years (IQR 1.9-9.2), 54% (n=465) were female. Median time to IPT initiation after enrollment in HIV care was 3.6 months (IQR=0.5-10.2). Sixty eight percent (n=559) of eligible CLHIV were initiated on IPT, 78% (n=434) of whom completed the 6-months regimen, 3% (n=16) transferred out, 18% (n=98) lost to follow-up, 2% (n=9) discontinued and <1% (n=1) was diagnosed with active TB. Correlates of non-initiation of IPT included age <5 years (aRR=1.22; 95% CI: 1.01-1.48) and viral non-suppression (aRR=9.78; 95% CI: 6.15-15.4). Viral non-suppression (aRR=4.21; 95% CI: 1.97-8.99) was also associated with non-completion of IPT among those who initiated. TB incidence was three-fold higher among CLHIV not initiated vs. initiated on IPT (13.0 vs. 3.7 per 1,000 child years, p=0.003), and among CLHIV who did not complete vs. completed IPT (8.1 vs. 2.6 per 1,000 child years, p-value=0.05).

**Conclusion:** While screening for IPT eligibility was high, later components of the IPT cascade (initiation and completion) were suboptimal. TB incidence at 24 months was higher among CLHIV who neither initiated nor completed IPT than those who completed IPT. There is need to strengthen IPT initiation and completion especially in virally non-suppressed CLHIV.

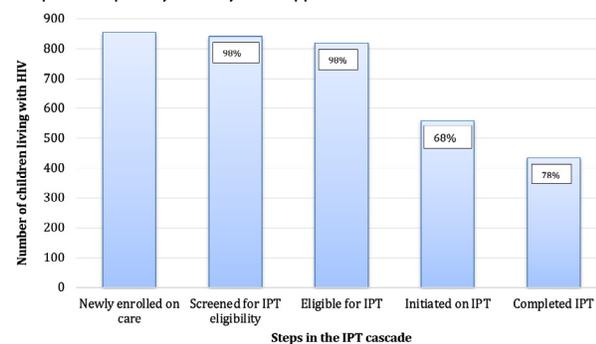


Figure 1: Isoniazid preventive therapy (IPT) cascade among children living with HIV newly enrolled in care in western Kenya, 2015-2019

## 561 RISK STRATIFICATION FOR IDENTIFYING OPTIMAL TREATMENT DURATION IN ALL MDR-TB PATIENTS

**Maria Garcia-Cremades**<sup>1</sup>, Natasha Strydom<sup>1</sup>, Jonathon R. Campbell<sup>2</sup>, Payam Nahid<sup>1</sup>, Dick Menzies<sup>2</sup>, Rada Savic<sup>1</sup>

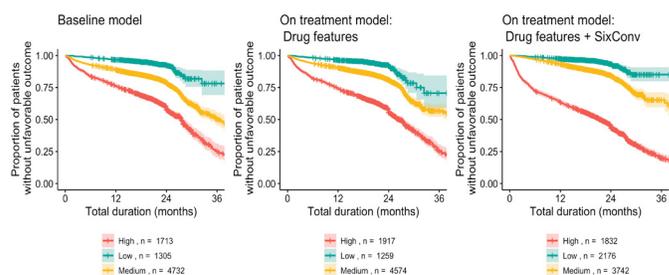
<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>McGill University, Montreal, Canada

**Background:** Multidrug-resistant tuberculosis (MDR-TB) requires extensive chemotherapy, with up to 2 years of treatment with toxic drugs. Using pooled individual patient data, we aimed to identify patient phenotypes who require shorter or longer treatment durations to optimize their chances of cure.

**Methods:** Published observational and experimental studies of MDR-TB treatment (12938 patients) were considered for analysis. Baseline clinical and treatment features, including drug given, duration and six-month culture conversion, were available. Patients who defaulted or were lost to follow up were excluded. Missing data were imputed using multivariate imputation via chained equations. Risk of unfavorable outcome, which included treatment failure and death, was analyzed through multivariate logistic regression models. We developed a baseline model, using baseline clinical predictors, and on treatment models, including additional treatment features predictors. Based on these models, the individual risk scores were computed, and patients were categorized in high (p<sub>unfavorable</sub>>50%), medium (15%<p<sub>unfavorable</sub><=50%) and low (p<sub>unfavorable</sub><15%) risk phenotypes.

**Results:** The final dataset included 5869 patients with treatment success, 628 patients with treatment failure, and 1253 patients who died. In the baseline model, HIV status was the most important predictor of TB unfavorable outcome (aOR 2.3; 95%CI [1.7, 3]; p<0.001). Previous treatment with second line drugs, older age, low BMI, smoking, AFB positivity, extrapulmonary involvement, cavitory disease and resistance to pyrazinamide, fluoroquinolones and injectable drugs were all associated with TB unfavorable outcome (p<0.05). In the on treatment models the use of linezolid, levofloxacin and bedaquiline were associated with lower odds of unfavorable outcome, while the use of kanamycin or capreomycin and PAS were associated with higher odds of unfavorable outcome (p<0.05). Six months culture conversion was the most significant predictor of treatment success. The proportion of patients without unfavorable outcome over treatment duration was significantly different between low, medium and high risk phenotypes (Figure 1).

**Conclusion:** We developed a risk stratification algorithm for patients with MDR-TB based on individual participant meta-analysis of a large dataset. Stratified medicine approaches where treatment duration is selected with greater precision for low, medium and high risk patient phenotypes will maximize chances for cure of all MDR-TB patients.



## 562 FINAL RESULTS OF THE NIX-TB CLINICAL STUDY OF BPaL REGIMEN FOR HIGHLY RESISTANT TB

**Francesca Conradie**<sup>1</sup>, Andreas Diacon<sup>2</sup>, Nosipho Ngubane<sup>1</sup>, Daniel Everitt<sup>3</sup>, Angela M. Crook<sup>4</sup>, Genevieve Wills<sup>4</sup>, Pauline J. Howell<sup>1</sup>, Jerry Nedelman<sup>3</sup>, Moroufolu Olugbosi<sup>5</sup>, Mengchun Li<sup>3</sup>, Joanna Moreira<sup>3</sup>, Eugene Sun<sup>3</sup>, Melvin Spigelman<sup>3</sup>

<sup>1</sup>University of Witwatersrand, Johannesburg, South Africa, <sup>2</sup>Stellenbosch University, Cape Town, South Africa, <sup>3</sup>Global Alliance for TB Drug Development, New York, NY, USA, <sup>4</sup>University College London, London, UK, <sup>5</sup>Global Alliance for TB Drug Development, Pretoria, South Africa

**Background:** Nix-TB was a single arm prospective study of a regimen of bedaquiline (400 mg daily for 2 weeks followed by 200 mg 3 times a week), pretomanid (200 mg per day) and linezolid (1200 mg per day starting dose, with dose modifications allowed after the first month), given orally for 6 months for Extensively Drug-Resistant (XDR) or treatment intolerant or failed Multidrug-Resistant (MDR) tuberculosis (TB). We report here on long-term efficacy and safety from the recently completed 24-month post-treatment followup in all patients.

**Methods:** We report the study's secondary endpoint of bacteriologic or clinical failure or relapse at 24 months post-treatment. Peripheral neuropathy associated with linezolid was assessed serially with standard symptoms rated from none (0) to worst (10) with a change from baseline score calculated at end of treatment and 24 months post-treatment. Detailed methods and the primary endpoint at 6 months after completion of therapy have been reported: <https://www.nejm.org/doi/full/10.1056/NEJMoa1901814>.

**Results:** At three South African sites 109 participants (65% XDR-TB, 35% MDR-TB; 51% HIV+) were enrolled and comprised the ITT population. 107 were included in the MITT population. All surviving patients, except 1 withdrawal, completed the full course of therapy. At the primary endpoint six months after treatment, as previously reported, there were 98 with favorable outcomes (90% ITT, 92% MITT). After the primary endpoint one patient relapsed 15 months after treatment and one was lost to follow up. Favorable outcomes 24 months post completion of treatment were sustained (88% ITT, 91% MITT) independent of sex or HIV status. A baseline score of 0 in the key neuropathy symptom question "pain, aching, burning of feet and legs" was found in 89 of 107 participants with baseline scores (83%). Of these 89, 83 had scores at an end of treatment visit that occurred at or after month 6, of whom 31 (37%) had positive scores, with 6 (7%) scoring 8-10. Of those 31, 29 had scores at the 24-month-post-treatment-follow-up visit, of whom 6 (21%) had positive scores, with none scoring 8-10.

**Conclusion:** Results of this simplified, shortened all oral regimen for highly drug resistant TB show sustained high efficacy through 2-year follow-up from end of treatment. Neuropathy from linezolid was common but improved over 24 months of follow-up. A follow-on trial, ZeNix, that investigates the optimal dose and duration of linezolid in the BPaL regimen, has completed enrollment.

**563 VALIDATION OF CLINIC-BASED POINT-OF-CARE TESTING FOR CRYPTOCOCCAL ANTIGEN SCREENING**

**Sean Galagan<sup>1</sup>, Sabina Govere<sup>2</sup>, Meighan Krows<sup>1</sup>, Hilary Thulare<sup>2</sup>, Carole Wallis<sup>3</sup>, Bernadette Gosnell<sup>4</sup>, Mahomed-Yunus Moosa<sup>4</sup>, Ingrid V. Bassett<sup>5</sup>, Connie L. Celum<sup>1</sup>, Paul K. Drain<sup>1</sup>**

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>AIDS Healthcare Foundation, Durban, South Africa, <sup>3</sup>BARC-SA & Lancet Laboratories, Johannesburg, Gauteng, South Africa, <sup>4</sup>University of KwaZulu-Natal, Durban, South Africa, <sup>5</sup>Massachusetts General Hospital, Boston, MA, USA

**Background:** Cryptococcus is a leading cause of death among people living with HIV. Clinic-based rapid testing may expedite prophylaxis to prevent meningitis and mortality. The objective of this analysis was to determine the diagnostic accuracy of a cryptococcal antigen (CrAg) lateral flow assay (LFA) when tested at the clinical point-of-care among HIV+ individuals with low CD4 count.

**Methods:** We screened non-pregnant adults 18+ years of age seeking voluntary HIV testing at iThembalabantu clinic in Umlazi Township, South Africa from November 2017 to February 2019. Participants testing HIV+ and consenting to participate were enrolled, completed a demographic survey and clinical assessment, and received a clinic-based rapid CD4 test. Among those with CD4 count  $\leq 200$  cells/mm<sup>3</sup>, a trained nurse conducted clinic-based CrAg LFA screening (Immy Diagnostics, Norman, USA) and collected a blood sample for gold-standard laboratory-based enzyme immunoassay (EIA) CrAg testing at the BARC lab (Johannesburg, South Africa). Diagnostic performance was assessed by calculating sensitivity, specificity, and positive and negative predictive values compared to gold-standard serum CrAg EIA.

**Results:** Among 1,493 eligible participants screened, 720 (48.2%) tested HIV+ and received rapid CD4 testing. Of the 164 participants with CD4 count  $\leq 200$  cells/mm<sup>3</sup>, all received clinic-based CrAg LFA testing and 162 had gold-standard CrAg EIA testing. CrAg prevalence was 6.1% by serum CrAg LFA and 4.9% by serum CrAg EIA. Serum CrAg LFA testing correctly identified seven of eight CrAg positives by EIA (87.5%, 95% confidence interval [CI]: 50.8-99.9%); specificity was 98.1% (CI: 94.2-99.6%) with three false positives and one false negative. The positive predictive value was 70.0% (CI: 39.2-89.7%) and negative predictive value was 99.3% (CI: 96.0-100.0%) (Table). Diagnostic performance was similar among participants with a CD4 count  $< 100$  cells/mm<sup>3</sup>.

**Conclusion:** Serum CrAg LFA delivered at the point-of-care showed high diagnostic accuracy compared to the gold-standard CrAg EIA, though with a lower positive predictive value suggesting the need for confirmatory testing. These results indicate that serum CrAg LFA may be feasible and accurate to perform at the clinical point-of-care to more rapidly identify HIV+ patients with cryptococcal antigenemia and intervene to prevent meningitis and mortality.

**Table.** Diagnostic performance of the clinic-based serum CrAg LFA against gold standard, laboratory-based serum CrAg EIA.

| CD4 count                        | #TP/<br>(#TP+#FN) | Sensitivity:<br>% (CI) | #TN/<br>(#TN+#FP) | Specificity:<br>% (CI) | PPV:<br>% (CI)   | NPV:<br>% (CI)     |
|----------------------------------|-------------------|------------------------|-------------------|------------------------|------------------|--------------------|
| $\leq 200$ cells/mm <sup>3</sup> | 7/8               | 87.5 (50.8-99.9)       | 151/154           | 98.1 (94.2-99.6)       | 70.0 (39.2-89.7) | 99.3 (96.0-100.0)  |
| $< 100$ cells/mm <sup>3</sup>    | 2/2               | 100.0 (29.0-100.0)     | 60/62             | 96.8 (88.3-99.8)       | 50.0 (15.0-85.0) | 100.0 (92.8-100.0) |

CI: 95% confidence interval, CrAg: cryptococcal antigen, EIA: enzyme immunoassay, FN: false negative, FP: false positive, LFA: lateral flow assay, NPV: negative predictive value, PPV: positive predictive value, TN: true negative, TP: true positive.

**564 POINT-OF-CARE CRYPTOCOCCAL ANTIGEN SCREENING FOR PREVENTING MENINGITIS AND MORTALITY**

**Paul K. Drain<sup>1</sup>, Sean Galagan<sup>1</sup>, Sabina Govere<sup>2</sup>, Meighan Krows<sup>1</sup>, Hilary Thulare<sup>2</sup>, Carole Wallis<sup>3</sup>, Bernadette Gosnell<sup>4</sup>, Mahomed-Yunus Moosa<sup>4</sup>, Connie L. Celum<sup>1</sup>, Ingrid V. Bassett<sup>5</sup>**

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>AIDS Healthcare Foundation, Durban, South Africa, <sup>3</sup>BARC-SA and Lancet Laboratory, Johannesburg, South Africa, <sup>4</sup>University of KwaZulu-Natal, Durban, South Africa, <sup>5</sup>Massachusetts General Hospital, Boston, MA, USA

**Background:** Cryptococcosis remains a leading cause of meningitis and mortality among people living with HIV worldwide. This study sought to evaluate laboratory-based cryptococcal antigen (CrAg) reflex testing and a clinic-based point-of-care (POC) CrAg screening intervention for preventing meningitis and mortality.

**Methods:** We conducted a prospective pre-post intervention study of adults presenting for HIV testing in Umlazi Township, South Africa. Participants were enrolled during three phases of CrAg testing – CrAg testing ordered by a clinician ("Clinician-directed testing"; 2013-2015); routine lab-based CrAg reflex testing for blood samples with CD4  $< 100$  cells/mm<sup>3</sup> ("Lab reflex testing"; 2015-2017), and a clinic-based intervention with POC CD4 testing and POC CrAg testing among persons with CD4  $\leq 200$  cells/mm<sup>3</sup>, in addition to background standard of care routine reflex testing among those with CD4  $< 100$  cells/mm<sup>3</sup> ("Clinic-based testing"; 2017-2019). The laboratory and clinical teams performed serum CrAg by enzyme immunoassay and lateral flow assay (Immy Diagnostics, Norman, USA). We followed participants for up to 14 months to assess the outcomes of ART and fluconazole treatment initiation, cryptococcal meningitis, hospitalization and mortality by baseline CrAg positivity.

**Results:** 3,105 (39.4%) of 7,877 people screened were HIV-positive, of whom 908 had CD4  $\leq 200$  cells/mm<sup>3</sup> and were included in analyses. Compared to clinician-directed testing, lab reflex and clinic-based testing increased CrAg screening ( $p < 0.001$ ) and diagnosis of Cryptococcus (CrAg+) ( $p = 0.020$ ).

Compared to clinician-directed testing, clinic-based CrAg testing increased the number of participants diagnosed with cryptococcal meningitis ( $p = 0.038$ ). Comparing clinic-based testing to lab reflex testing, there was no significant difference in the cumulative incidence of cryptococcal meningitis (4.5% compared to 4.1%;  $p = 0.829$ ) or mortality (8.1% compared to 9.9%;  $p = 0.463$ ).

**Conclusion:** Among ambulatory adults recently diagnosed with HIV in South Africa, lab reflex and clinic-based CrAg testing facilitated diagnosis of HIV-associated cryptococcosis and fluconazole initiation, compared to clinician-directed CrAg testing. Clinic-based CrAg testing increased the number diagnosed with cryptococcal meningitis, but did not alter hospitalization or mortality rates. In this non-randomized cohort, clinical outcomes were similar between lab reflex testing and clinic-based point-of-care CrAg testing.

**Table.** Clinical outcomes by study phase.

| Post-baseline clinical outcomes                     | Total<br>(N=908)<br>n (%) | Intervention group                       | Standard-of-Care groups                        |  | p*         | p*    |
|---|---------------------------|--|--|--|------------|-------|
|   |                           | Clinic-based testing<br>(N=222)<br>n (%) | Clinician-directed<br>testing (N=323)<br>n (%) | Lab reflex<br>testing (N=363)<br>n (%) |            |       |
| <b>Primary outcomes</b>                             |                           |  |  |  |            |       |
| Cryptococcal meningitis diagnosis                   | 30 (3.3)                  | 10 (4.5)                                 | 5 (1.5)  | <b>0.038</b>                           | 15 (4.1)   | 0.829 |
| All-cause hospitalization                           | 98 (10.8)                 | 21 (9.5)                                 | 28 (8.7)                                       | 0.751                                  | 49 (13.5)  | 0.144 |
| All-cause mortality                                 | 85 (9.4)                  | 18 (8.1)                                 | 31 (9.6)                                       | 0.550                                  | 36 (9.9)   | 0.463 |
| <b>Secondary outcomes</b>                           |                           |  |  |  |            |       |
| Hospitalization due to known cryptococcal infection | 11 (1.2)                  | 4 (1.8)                                  | 4 (1.2)  | 0.591                                  | 3 (0.8)    | 0.292 |
| Mortality due to known cryptococcal infection       | 9 (1.0)                   | 4 (1.8)                                  | 1 (0.3)  | 0.073                                  | 4 (1.1)    | 0.479 |
| Initiation of antiretroviral therapy                | 850 (93.6)                | 215 (96.8)                               | 295 (91.3)                                     | <b>0.010</b>                           | 340 (93.7) | 0.090 |
| Received fluconazole preventative therapy**         | 46 (5.1)                  | 16 (7.2)                                 | 8 (2.5)  | <b>0.008</b>                           | 22 (6.1)   | 0.585 |
| Received intravenous amphotericin-B                 | 8 (0.9)                   | 3 (1.4)                                  | 4 (1.2)  | 0.508                                  | 1 (0.3)    | 0.125 |
| Lost to follow-up                                   | 113 (12.4)                | 16 (7.2)                                 | 56 (17.3)                                      | <b>0.001</b>                           | 41 (11.3)  | 0.106 |

\* p-value represents a Chi<sup>2</sup> test of the comparison between each standard of care group with the intervention group.

\*\* Oral fluconazole was indicated for people with serum cryptococcal antigenemia, but without cryptococcal meningitis.

**565 CRYPTOCOCCAL MENINGITIS AND CLINICAL OUTCOMES IN PERSONS WITH HIV ACROSS THE GLOBE**

**Anna Person**<sup>1</sup>, Brenda Crabtree Ramirez<sup>2</sup>, Ahra Kim<sup>3</sup>, Fernanda Maruri<sup>3</sup>, Gilles Wandeler<sup>4</sup>, Richard Moore<sup>5</sup>, Darma Imran<sup>6</sup>, Kinh Van Nguyen<sup>7</sup>, Elizabeth Nalinya<sup>8</sup>, Winnie Muyindike<sup>9</sup>, Bryan Shepherd<sup>3</sup>, Catherine McGowan<sup>3</sup>, for leDEA  
<sup>1</sup>Vanderbilt University, Nashville, TN, USA, <sup>2</sup>Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico City, Mexico, <sup>3</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>4</sup>Bern University Hospital, Bern, Switzerland, <sup>5</sup>The Johns Hopkins Hospital, Baltimore, MD, USA, <sup>6</sup>Cipto Mangunkusumo Hospital, Jakarta, Indonesia, <sup>7</sup>National Hospital of Tropical Diseases, Hanoi, Vietnam, <sup>8</sup>Infectious Diseases Institute, College of Health Sciences, Makerere University, Kampala, Uganda, <sup>9</sup>Mbarara University of Science and Technology, Mbarara, Uganda

**Background:** Cryptococcal meningitis (CM) is a major cause of morbidity and mortality in persons with HIV (PWH). Few studies have examined CM in PWH after expanded global implementation of ART.

**Methods:** This retrospective cohort study investigated CM incidence and all-cause mortality after CM diagnosis among PWH ≥16 years of age enrolled in an leDEA cohort from 1996-2017. Incidence and incidence rate ratios (IRRs) for CM diagnosis were estimated by leDEA region (North America[NA], Asia-Pacific[AP], Latin America[LA], East Africa[EA], and Southern Africa[SA]), sex, calendar year, time-updated CD4 count, and time-updated ART status using multivariable Poisson regression. Hazard ratios (HRs) for mortality after CM diagnosis were examined using Kaplan-Meier and multivariable Cox regression.

**Results:** Among 819,641 PWH followed a median of 2.8 years from clinic enrollment, 3961 (0.5%) were diagnosed with CM (incidence 1.15 per 1000 person-years[py]). Incidence over follow-up period per 1000py varied across regions: 0.89 (95% CI 0.69-1.16) in NA, 0.58 (95% CI 0.15-2.24) in AP, 2.17 (95% CI 1.34-3.52) in LA, 2.08 (95% CI 1.77-2.45) in EA, and 0.42 (95% CI 0.30-0.60) in SA. Unadjusted incidence decreased by calendar year: 1.46/1000py (95% CI 0.46-4.61) in 2000 vs. 0.62 (95% CI 0.34-1.11) in 2015. Current ART use (IRR 0.33, 95% CI 0.25-0.44) and higher CD4 (IRR 3.82 comparing 200 vs. 350 cells/mm<sup>3</sup>, 95% CI 3.09-4.72) were associated with lower risk of CM (Figure). Of 3961 diagnosed with CM, 1401 were diagnosed before ART start and 2560 (65%) were diagnosed after ART start, with a median time of 255 days from ART start to CM diagnosis (IQR: 56, 1051); 1237 (31%) with CM died during follow-up and 1401 (35%) were lost to follow-up. Estimated probability of death 2 years after CM diagnosis was 24% (95% CI 0.22-0.26) for those on ART vs. 29% (95% CI 0.27-0.32) for those not on ART at diagnosis. Older age at enrollment (HR=1.29 for 50 vs. 35 years; 95% CI 1.11-1.51), lower CD4 count at CM diagnosis (HR=1.15 for 200 vs. 350; 95% CI 1.03-1.28), and earlier year of diagnosis (HR=0.60 for 2015 vs. 2000; 95% CI 0.49-0.73) were associated with higher risks of mortality.

**Conclusion:** Despite potential limitations of unequal ascertainment across regions and high loss to follow-up, incidence of CM has decreased globally but remains critically associated with mortality for PWH, with highest incidence in Latin America. A substantial proportion of CM cases occurred after ART start.

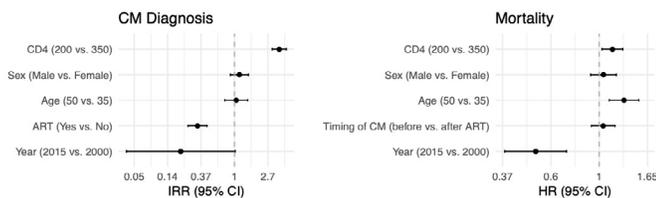


Figure. Incidence rate ratios (IRRs) for cryptococcal meningitis (CM) diagnosis (left panel) and hazard ratios (HR) for all-cause mortality after CM diagnosis (right panel) in the leDEA cohort from 1996-2017.

**Methods:** The Mobile WACH3-arm unblinded randomized trial (RCT) compared 2-way and 1-way SMS messaging to no SMS control. We adapted an existing MCH SMS platform to incorporate antiretroviral therapy (ART) adherence messages based on the Health Belief Model and Social Cognitive Theory. ART and MCH SMS were sent weekly; visit reminders were sent 3 days before appointments. Participants at 6 MCH clinics in Nairobi and Western Kenya were enrolled in pregnancy, randomized, and followed until 24 months postpartum. Clinic attendance, viral load (VL), and infant HIV test results were abstracted from clinic records. Primary outcomes were viral non-suppression (VL ≥1000 c/ml), on-time clinic attendance (within 2 weeks), loss to follow-up (≥6 months out of care), and infant HIV-free survival. Intent-to-treat analyses compared arms using generalized estimating equations and Cox regression, adjusted for baseline differences.

**Results:** Overall 824 pregnant women were randomized (271 2-way, 276 1-way, 277 control). Median age was 27 years (Interquartile Range (IQR) 23-31), gestational age was 24.3 weeks (IQR 18.3-29.6), and time since ART initiation was 1.00 year (IQR 0.02-3.21). During follow-up to 24 months postpartum, 9.78% of 3150 VL assessments were unsuppressed. There were no differences in frequency of non-suppression in 1-way vs. control (adjusted Risk Ratio (aRR) 1.02 [95% Confidence Interval (CI) 0.67-1.54]) or 2-way vs. control (aRR 0.80 [95% CI 0.52-1.23]) (Table 1). Overall, 88.9% (95% CI 76.5-95.7) of visits were on-time, with no difference in 1-way vs. control (aRR 1.00 [95% CI 0.98-1.03]) or 2-way vs. control (aRR 1.01 [95% CI 0.99-1.04]). Incidence of infant HIV acquisition or death during follow-up was 3.01/100py, with no difference in 1-way vs. control or 2-way vs. control arms; overall HIV transmission risk was 0.94%.

**Conclusion:** In this multi-site RCT in Kenyan PMTCT programs, MTCT was rare despite appreciable maternal viral non-suppression. Integrated HIV/MCH messaging did not improve clinic attendance or viral suppression. Potential reasons for lack of effect include high baseline clinic attendance or low impact of generic adherence message. Tailoring SMS to real-time VL results may enhance relevance.

Table 1

|  | Overall (N=824)  | Control (N=277)  | One-way (N=271)  | Two-way (N=276)  | One-way vs control   | Two-way vs control   |
|--|------------------|------------------|------------------|------------------|--|--|
| <b>Viral non-suppression (≥1000c/ml) after ≥4 months on ART</b>                      |                  |                  |                  |                  |  |  |
| Frequency of post-enrollment viral non-suppression (VL NS) n unsuppressed / n VL (%) |                  |                  |                  |                  | RR (95% CI), p-value   |  |
| N participants   | 727              | 243              | 235              | 249              |  |  |
| VL NS at any time  | 308/3150 (9.78)  | 99/1029 (9.62)   | 119/1066 (11.20) | 90/1055 (8.53)   | cRR: 1.09 (0.73-1.65), p=0.67<br>aRR: 1.02 (0.67-1.54), p=0.94 | cRR: 0.87 (0.56-1.34), p=0.53<br>aRR: 0.80 (0.52-1.23), p=0.31 |
| <b>Timely attendance</b>   |                  |                  |                  |                  |  |  |
| Proportion of scheduled visits attended within 2 weeks (%; 95% CI)                   |                  |                  |                  |                  | RR (95% CI), p-value   |  |
| N participants   | 794              | 268              | 264              | 262              |  |  |
| Attendance by 1 year postpartum  | 90.0 (75.0-100)  | 88.9 (75.0-100)  | 90.9 (75.0-100)  | 90.9 (71.4-100)  | cRR: 1.00 (0.98-1.03), p=0.85<br>aRR: 1.01 (0.98-1.04), p=0.52 | cRR: 1.00 (0.98-1.03), p=0.84<br>aRR: 1.01 (0.98-1.04), p=0.55 |
| Attendance by 2 years postpartum   | 88.9 (76.5-95.7) | 88.9 (77.6-95.5) | 88.9 (75.0-95.7) | 89.5 (75.0-95.7) | cRR: 1.00 (0.97-1.02), p=0.78<br>aRR: 1.00 (0.98-1.03), p=0.81 | cRR: 1.00 (0.98-1.03), p=0.70<br>aRR: 1.01 (0.99-1.04), p=0.36 |
| <b>Loss to follow-up</b>   |                  |                  |                  |                  |  |  |
| N participants   |                  |                  |                  |                  | HR (95% CI), p-value   |  |
| N participants   | 813              | 276              | 270              | 267              |  |  |
| n events   | 183              | 58               | 62               | 63               | cHR: 1.08 (0.75-1.54), p=0.68<br>aHR: 0.99 (0.69-1.42), p=0.97 |  |
| n py   | 1349.0           | 450.7            | 447.8            | 450.5            | cHR: 1.11 (0.77-1.58), p=0.58<br>aHR: 1.02 (0.71-1.47), p=0.90 |  |
| IR/100 py  | 13.6             | 12.9             | 13.8             | 14.0             |  |  |
| <b>Infant HIV-acquisition or death</b>   |                  |                  |                  |                  |  |  |
| N participants   |                  |                  |                  |                  | HR (95% CI), p-value   |  |
| N participants   | 744              | 252              | 240              | 252              |  |  |
| N events   | 44               | 13               | 11               | 20               | cHR: 0.89 (0.40-1.98), p=0.77<br>aHR: 0.83 (0.37-1.87), p=0.66 |  |
| N py   | 1460.65          | 501.79           | 475.83           | 483.03           | cHR: 1.57 (0.78-3.15), p=0.20<br>aHR: 1.44 (0.71-2.92), p=0.31 |  |
| IR/100 py  | 3.01             | 2.59             | 2.31             | 4.14             |  |  |
| N HIV+   | 7                | 1                | 1                | 5                |  |  |

cRR crude risk ratio; aRR adjusted risk ratio; cHR crude hazard ratio; aHR adjusted hazard ratio; py person-year; IR incidence rate. Adjusted models include employment and primigravida.

**566 RCT OF 2-WAY VS 1-WAY SMS MESSAGING TO IMPROVE EFFICACY OF PMTCT-ART IN KENYA**

**John Kinuthia**<sup>1</sup>, Keshet Ronen<sup>2</sup>, Jennifer A. Unger<sup>2</sup>, Wenwen Jiang<sup>2</sup>, Daniel Matemo<sup>1</sup>, Trevor Perrier<sup>2</sup>, Osborn Lusi<sup>1</sup>, Bhavna Chohan<sup>3</sup>, Alison L. Drake<sup>2</sup>, Barbra A. Richardson<sup>2</sup>, Grace John-Stewart<sup>2</sup>  
<sup>1</sup>Kenyatta National Hospital, Nairobi, Kenya, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>Kenya Medical Research Institute, Nairobi, Kenya

**Background:**

Prevention of mother-to-child HIV transmission (PMTCT) requires sustained maternal retention and viral suppression. We hypothesized that integrating HIV messages within a maternal child health (MCH) short messaging system (SMS) platform could improve retention and viral suppression.

**567 IMPACT OF MODIFIED STANDARD-OF-CARE FOR VIROLOGIC FAILURE IN ART-EXPERIENCED WOMEN**

**Mercy T. Mutambanengwe-Jacob**<sup>1</sup>, Tendayi Goverayi<sup>1</sup>, Tariro D. Chawana<sup>1</sup>, Petronella Matibe<sup>1</sup>, Bernadette V. Malunda<sup>1</sup>, Mary G. Fowler<sup>2</sup>, Taha E. Taha<sup>2</sup>, Tsungai Chipato<sup>1</sup>, K. Rivet Amico<sup>3</sup>, Charles C. Mponga<sup>1</sup>, Justice F. Gumbo<sup>1</sup>, Nonhlanhla Yende-Zuma<sup>4</sup>, Jim Aizire<sup>2</sup>, Lynda Stranix-Chibanda<sup>1</sup>, for the Zimbabwe PROMOTE Study Team

<sup>1</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>2</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>3</sup>University of Michigan, Ann Arbor, MI, USA, <sup>4</sup>Centre for the AIDS Programme of Research in South Africa, Durban, South Africa

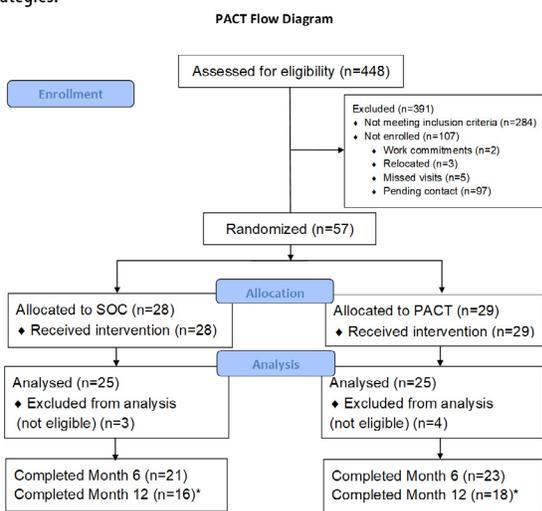
**Background:** Targeting sustained HIV viral suppression, we assessed the combined effectiveness of point-of-care viral load monitoring plus motivational adherence counselling (POCVL+MAC) compared with routine care in ART-

experienced peripartum women identified to be at risk of virologic failure in the PROMOTE study in Zimbabwe.

**Methods:** Women with last viral load  $\geq 200$  copies/ml and/or pill count outside 90-110% of expected were considered at risk of virologic failure. After tracing, consenting women were randomized 1:1 to continue lab-based viral load monitoring and routine adherence counseling (control) or receive POCVL+MAC from trained primary care nurses and counsellors. Viral load was measured at 0, 3, 6 and 12 months post enrolment. Viral suppression  $< 200$  copies/ml at 6 months (primary outcome) was compared between arms through Chi-square testing, and associated factors sought by logistic regression with a 95% confidence interval (CI).

**Results:** Of 448 women screened from December 2018 to July 2019, 157 met the risk criteria; 119 by pill count alone, 38 by last viral load (11/38 also by pill count). 50 women were enrolled (25 control, 25 POCVL+MAC); mean (sd) age was 33 (6) years and 49/50 (98%) were on NNRTI-based ART for an average (sd) duration of 3 (1) years. Baseline sociodemographic characteristics were comparable across arms. At entry, 30 women (60%) had viral suppression; 68% control, 52% POCVL+MAC (Chi2 1.33, p=0.248). At 6 months, only 28 of the 44 retained had viral suppression (64%); 16/21 (76%) control, 12/23 (52%) POCVL+MAC (Chi2 2.74, p=0.098). More POCVL+MAC than control women completed all scheduled counselling and testing sessions; 7/12(58%) POCVL+MAC, 1/9 (11%) control. Control group women were more likely to be virally suppressed at month 6 (OR 2.93, 95%CI 0.80-10.71). Higher education OR 5.00 (CI 0.56-45.02), pill count averaging 100% OR 1.03 (CI 0.97-1.08), more than 60minutes travel time to clinic OR 1.75 (CI 0.34-8.98) and HIV disclosure OR 1.59 (CI 0.14-17.56) were associated with an unsuppressed viral load. Only 2 (14%) had treatment switch at or by 6 months, one in each arm.

**Conclusion:** Sustained viral suppression remained elusive in ART-experienced peripartum women identified at risk of viral failure after a 6-month enhanced adherence program. Despite full intervention delivery, POCVL+MAC did not significantly improve viral suppression. There is need to explore other causes of viral un-suppression such as drug resistance, and improve on treatment switch strategies.



**568 MATERNAL VL TESTING IN BREASTFEEDING FOR TARGETED INFANT HIV TESTING: A SIMULATION**

**Maia Lesosky<sup>1</sup>**, Elaine J. Abrams<sup>2</sup>, Tracy Glass<sup>1</sup>, Mustafa Shuaib<sup>1</sup>, Janet Raboud<sup>3</sup>, Andrea Ciaranello<sup>4</sup>, Shaffiq Essajee<sup>5</sup>, Diane V. Havli<sup>6</sup>, Catherine A. Koss<sup>6</sup>, Anthony Ogwu<sup>7</sup>, Roger Shapiro<sup>4</sup>, Lara Vojnov<sup>8</sup>, Landon Myer<sup>1</sup>

<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>Columbia University Medical Center, New York, NY, USA, <sup>3</sup>University Health Network, Toronto, Canada, <sup>4</sup>Harvard Medical School, Boston, MA, USA, <sup>5</sup>United Nations Children's Fund, New York, NY, USA, <sup>6</sup>University of California San Francisco, San Francisco, CA, USA, <sup>7</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>8</sup>World Health Organization, Geneva, Switzerland

**Background:** Challenges encountered by women during the postpartum period contribute to poor ART adherence leading to elevated maternal viral load (VL). In high-burden settings where at least 12m breastfeeding is recommended, this raises concerns about ongoing MTCT; enhanced VL monitoring during

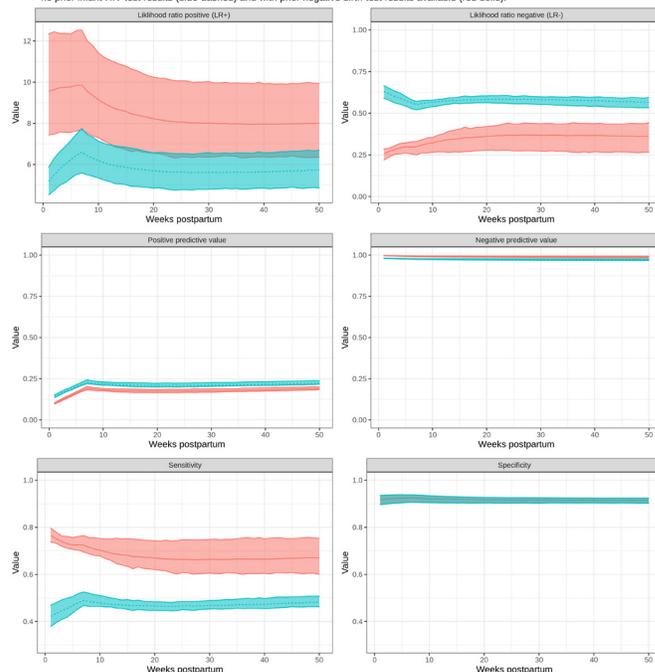
breastfeeding is widely discussed but there is little understanding of how detection of maternal viraemia is associated with infant HIV transmission risk.

**Methods:** We used an established Monte Carlo simulation of maternal VL dynamics and MTCT during pregnancy and breastfeeding, calibrated using best available data. Maternal VL was simulated in cohorts of 50,000 women from conception through 2 years postpartum, with a breastfeeding duration of at least 12m postpartum. We used this simulation to estimate, by infant age and maternal VL over time, the ability of maternal VL values to predict cumulative risk of infant HIV transmission. Results are expressed as positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratios (LR+ and LR-). Sensitivity analyses varied distributions of maternal ART use prior to conception and levels of maternal viraemia, and incorporated hypothetical information on previous infant HIV testing at birth and 6 weeks of age.

**Results:** In the base simulation, 50% of women were on ART prior to conception and 50% initiated during pregnancy at median 20 weeks gestation. 89% of women had VL  $< 50$  cps/mL at delivery, 6% of women never achieved VL  $< 50$  cps/mL through 2 years postpartum, and 21% of women experienced VL  $> 1000$  cps/mL postpartum after prior VL  $< 50$  cps/mL. Cumulative MTCT risks were 2.0% at birth, 3.5% at 6w and 4.4% at 12m postpartum. Breastfeeding maternal VL  $> 1000$  cps/mL had low PPVs (5%-25%) in predicting cumulative infant HIV infection, while NPV were  $> 96%$  in all scenarios. LR+ ranged from 2.5 to 12.5 and were stable across infant ages, with higher values observed in scenarios where an infant was known to have a negative HIV test result at birth (Figure). LR- were lowest ( $< 0.3$ ) for infants with HIV- birth testing but increased over time. Analogous results were observed when using VL thresholds of 10,000 cps/mL and findings were robust to variation in key parameters.

**Conclusion:** Elevated maternal VL observed during breastfeeding becomes more useful as a predictive tool for targeted infant testing when combined with information about prior infant HIV negative test results.

Diagnostic measures for a single maternal viral load  $> 1000$  copies/mL in predicting infant HIV infection at the time of maternal VL testing, by weeks postpartum. Plots are shown with 90% uncertainty intervals. Separate curves are shown for analysis of infants with no prior infant HIV test results (blue-dashed) and with prior negative birth test results available (red-solid).



**569 ANTIRETROVIRAL THERAPY ADHERENCE DURING & POST BREASTFEEDING USING TFV LEVELS IN HAIR**

**Teader G. Nematadzira<sup>1</sup>**, Pamela Murnane<sup>2</sup>, Peter Bacchetti<sup>2</sup>, Hideaki Okochi<sup>2</sup>, Regina Tallerico<sup>2</sup>, Alexander Louie<sup>2</sup>, Vongai M. Chanaiwa<sup>1</sup>, Tichaona Vhembo<sup>1</sup>, Mercy T. Mutambanengwe-Jacob<sup>1</sup>, Tsungai Chipato<sup>1</sup>, Monica Gandhi<sup>2</sup>, Lynda Stranix-Chibanda<sup>1</sup>, for the PROMISE Study Team

<sup>1</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA

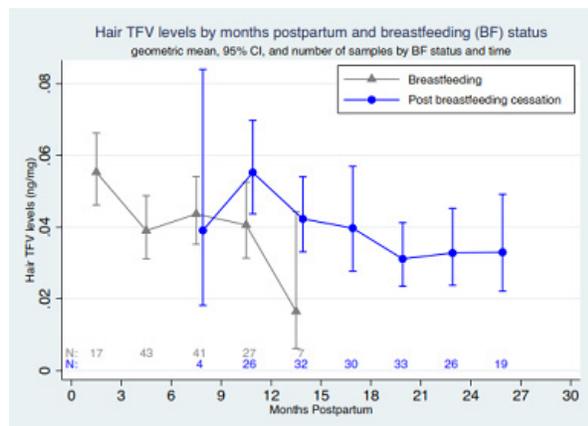
**Background:** The period post breastfeeding (BF) cessation is vulnerable to attrition and declining adherence to antiretroviral treatment (ART) among women with HIV. Antiretroviral concentrations in hair reflect cumulative

exposure over weeks to months. We assessed if ART adherence declined among postpartum women after the risk of transmitting HIV to their infants was over, using hair tenofovir (TFV) levels as an objective metric of medication consumption. Moreover, we estimated the association between hair TFV levels and viremia.

**Methods:** A subset of women randomized in the PROMISE Study to take ART while BF and continue ART post BF cessation participated in the Hair Substudy in Zimbabwe. Hair and viral loads were collected longitudinally throughout follow-up. Hair TFV levels were measured via validated methods in samples collected after >45 days of TFV-containing ART. We estimated the impact of BF cessation on hair TFV levels via mixed linear models adjusted for demographics, prior viremia and timing of ART initiation. Also, we estimated the relative risk of viremia (>400 copies/mL) associated with each doubling of hair TFV level.

**Results:** Of the 55 women in this analysis (age 19–41), 93% were asymptomatic (WHO Stage I). Hair TFV results (n=305) were available a median of 9 visits/woman from 3–29 months postpartum (up to 1 year post BF cessation). TFV levels were highly variable over time (Figure; median 0.04 ng/ml, range undetectable–0.25 across all samples). In adjusted analyses, we observed a non-significant decline in TFV levels after delivery (–1%/month, 95%CI –4,1). TFV levels were 25% higher (95%CI 1.55; p=0.04) post BF cessation than during BF, coupled with a further non-significant 1% monthly decline in TFV levels (95%CI –4,2). 14/55 (25%) women were ever viremic postpartum, reaching a median of 15,564 copies/mL (range: 571–81,562). High TFV levels were strongly protective of viremia: the relative risk of viremia per doubling of TFV was 0.43 (95%CI 0.27–0.68; p<0.0001).

**Conclusion:** Leveraging an objective metric of ART use during BF and after cessation, we did not observe declining adherence associated with BF cessation. ART adherence is challenging postpartum, and BF cessation may be an opportune time to reinforce adherence support. Varying TFV levels over time and across women throughout the postpartum period highlight the importance of differentiated care for women needing additional support throughout these life transitions to achieve sustained viral suppression and eliminate pediatric HIV.



## 570 NRTI-SPARING STRATEGY TO PREVENT PERINATAL HIV TRANSMISSION, ANRS 168 MONOGEST TRIAL

**Laurent Mandelbrot**<sup>1</sup>, Roland Tubiana<sup>1</sup>, Pierre-Henri Frange<sup>1</sup>, Véronique Avettand-Fenoël<sup>1</sup>, Gilles Peytavin<sup>1</sup>, Ana Canestri<sup>1</sup>, Philippe Morlat<sup>2</sup>, Cécile Brunet<sup>3</sup>, Jeanne Sibuide<sup>1</sup>, Delphine Peretti<sup>1</sup>, Véronique Chambrin<sup>1</sup>, Amélie Chabrol<sup>4</sup>, Eida Bui<sup>1</sup>, Lucie Marchand<sup>5</sup>, Josiane Warszawski<sup>6</sup>

<sup>1</sup>Assistance Publique–Hôpitaux de Paris, Paris, France, <sup>2</sup>Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France, <sup>3</sup>CHU Nantes, Nantes, France, <sup>4</sup>Centre Hospitalier du Sud Francilien, Evry, France, <sup>5</sup>ANRS, Paris, France, <sup>6</sup>Institut National de la Santé et de la Recherche Médicale, Le Kremlin-Bicêtre, France

**Background:** Control of HIV viral load (VL) is effective prevention of perinatal transmission. Antiretroviral therapies (ART) include nucleoside reverse transcriptase inhibitors (NRTIs), but these can have side effects in the fetus. We evaluated a strategy with no NRTI during pregnancy, intrapartum and post-partum prophylaxis in women at low risk of HIV perinatal transmission. Our objective was to estimate, in women switching to darunavir/ritonavir monotherapy (DRV/r) early in pregnancy, the proportion maintaining a VL < 50 copies/mL at delivery, with no need of treatment reintensification.

**Methods:** A one-arm, open-label, phase 2 clinical trial was performed in 24 French centers. Women with virological suppression and CD4 ≥ 250 cells/μL were enrolled to treatment simplification with DRV/r (600/100 mg bid) in the 1st trimester of pregnancy. Plasma VL was monitored monthly and ART was reintensified in case of viral rebound (>50 copies/mL). Tolerance issues were managed per usual guidelines. Neonates received prophylaxis with nevirapine qd for 14 days. The trial was designed to investigate the virological success rate, with a 2-sided alpha=5% for the exact test comparing the observed proportion of VL<50 copies/mL on monotherapy against a minimum success rate set at p0=85% and an expected success rate of p1=95%, requiring 80 evaluable patients.

**Results:** Of 91 women enrolled, 89 switched to DRV/r monotherapy; 83 were evaluable, 4 miscarried before 22 weeks' gestation, and 2 changed because of elevated liver enzymes. Treatment was reintensified with NRTIs for viral rebound in not 6/83 (median VL 193 copies/mL; range 78–252), including 2 patients whose rebound occurred on triple ART after screening but before switching to DRV/r. Another 2 patients with VL missing at delivery were considered as failures in the primary per-protocol analysis, resulting in a success rate of 75/83, 90.4% (95%CI, 81.9–95.7%), not significantly above p0=85% (p=0.22). The 2 patients with missing delivery VL had undetectable values on DRV/r until 33 days and 13 days before delivery. If considering them as successes, success was 77/83 = 92.8% (95%CI, 84.9–97.3%), which was significantly higher than 85% (p=0.045). In an intent-to-treat analysis, all 89 women who switched to DRV/r monotherapy had their last VL before delivery < 50 copies/mL. There was no case of perinatal HIV transmission.

**Conclusion:** This pilot study suggests that a NRTI-free strategy with careful viral load surveillance can maintain viral suppression during pregnancy.

Table. Virological outcomes in ANRS 168 MONOGEST, n=89

|   | Pregnancy outcome ≥ 22 WG (N=85) |           | Pregnancy outcome < 22 WG (N=4) |       |
|---|----------------------------------|-----------|---------------------------------|-------|
|   | %                                | IC95%     | %                               | N     |
| <b>DRV/r monotherapy changed before delivery</b>    |                                  |           |                                 |       |
| No change   | 90.6                             | 82.3–95.8 | 100.0                           | (4)   |
| Changed for inefficacy                              | 7.1                              | (6)       | 0.0                             | (0)   |
| Changed for intolerance                             | 2.4                              | (2)       | 0.0                             | (0)   |
| <b>VL at pregnancy outcome (-8 to +7 days)</b>      |                                  |           |                                 |       |
| < 50 copies/mL                                      | 96.5                             | 90.0–99.3 | 75.0                            | (3)   |
| > 50 copies/mL                                      | 0.0                              | (0)       | 0.0                             | (0)   |
| Unknown at delivery (-8 to +7 days)                 | 3.5                              | (3*)      | 25.0                            | (1**) |
| <b>Last VL at, or before, delivery</b>              |                                  |           |                                 |       |
| < 50 copies/mL                                      | 100.0                            | 95.8–1    | 100.0                           | (4)   |
| <b>Primary endpoint among 83 evaluable patients</b> |                                  |           |                                 |       |
| <b>With missing VL at delivery = failure</b>        |                                  |           |                                 |       |
| Success   | 90.4                             | 81.9–95.7 | (75)                            |       |
| Failure (including 2 missing VL)                    | 9.6                              | (8)       |                                 |       |
| <b>With missing VL at delivery as success</b>       |                                  |           |                                 |       |
| Success (VL<50 with no DRV/r change)                | 92.8                             | 84.9–97.3 | (77)                            |       |
| Failure   | 7.2                              | (6)       |                                 |       |

\* 1 for consent withdrawal at 28 WG with last VL available at 26WG, 2 with last VL at 13 and 33 days before delivery (both <50 cp/mL)

\*\*Last Viral load available at 14 WG, 32 days before delivery

## 571 MATERNAL WEIGHT AND ADVERSE PREGNANCY OUTCOMES AMONG WOMEN ON ART AT CONCEPTION

**Rebecca Zash**<sup>1</sup>, Ellen Caniglia<sup>2</sup>, Modiegi Diseko<sup>3</sup>, Gloria Mayondi<sup>3</sup>, Judith Mabuta<sup>3</sup>, Rebecca Lockett<sup>1</sup>, Justus Hofmeyr<sup>4</sup>, Chelsea Morroni<sup>5</sup>, Doreen Ramogola-Masire<sup>6</sup>, Paige L. Williams<sup>7</sup>, Chloe Zera<sup>1</sup>, Joseph Makhema<sup>3</sup>, Shahin Lockman<sup>7</sup>, Roger Shapiro<sup>6</sup>

<sup>1</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA, <sup>2</sup>New York University Langone Medical Center, New York, NY, USA, <sup>3</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>4</sup>University of Botswana, Gaborone, Botswana, <sup>5</sup>University of Liverpool, Liverpool, UK, <sup>6</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>7</sup>Brigham and Women's Hospital, Boston, MA, USA

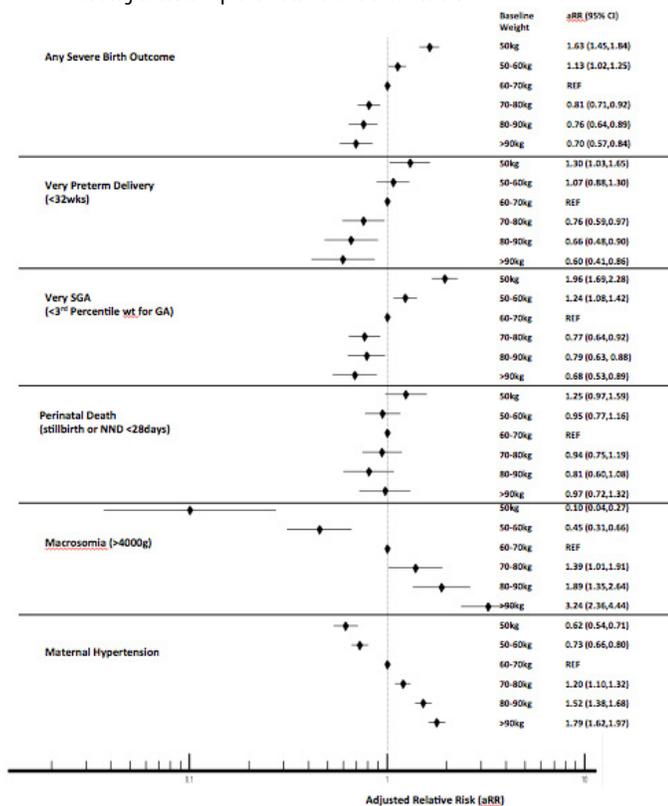
**Background:** Antiretrovirals such as dolutegravir (DTG) and tenofovir alafenamide (TAF) have been associated with excessive weight gain, but the impact of weight and weight gain on pregnancy outcomes is poorly described among women on antiretroviral treatment (ART).

**Methods:** Using data from the Tsepamo birth outcomes surveillance study in Botswana, we evaluated the relationship between maternal weight (and weight gain) and severe birth outcomes (very preterm delivery <32weeks, very small for gestational age <3rd percentile, perinatal death), macrosomia (birthweight >4000g) and maternal hypertension. We estimated the relative risk of each outcome by baseline weight (first weight in pregnancy <24 weeks) and second trimester average weekly weight gain (kg/week from 12 +/–2 to 24 +/–2 weeks)

using log binomial regression and evaluated effect modification by ART regimen (DTG vs. Efavirenz [EFV]).

**Results:** Of 22,828 women on ART at conception with singleton deliveries between August 2014–April 2020, 16,300 (71.4%) had a documented weight measured at <24 weeks gestation (baseline weight) and 4437 (19.2%) had documented weight measured both at 12 (+/-2) weeks and 24 (+/-2) weeks, allowing gestational weight gain calculation. Compared to women with baseline weight 60–70kg, low baseline weight (<50kg) was associated with increased risk of very preterm delivery (aRR 1.30, 95% CI 1.03,1.65) and very small for gestational age (aRR 1.96, 95% CI 1.69,2.28). High baseline weight (>90kg) was associated with increased risk of macrosomia (aRR 3.24, 95% CI 2.36,4.44) and maternal hypertension (aRR 1.79, 95% CI 1.62,1.97)(Figure 1). Baseline weight was not associated with perinatal death. For all outcomes, gestational weight gain showed weaker associations than did baseline weight. Duration of pre-pregnancy ART (years) was associated with higher baseline pregnancy weight for DTG but not for EFV, and the risk of maternal hypertension by baseline weight category was higher for DTG than EFV for all strata.

**Conclusion:** ART regimens associated with weight gain may reduce the percentage of low weight women at risk for certain severe adverse pregnancy outcomes but increase the number at risk of maternal hypertension. Further research is needed to determine whether weight-based ART treatment strategies could improve maternal and child health.



**572 PREDICTED LONG-TERM ADVERSE BIRTH AND CHILD HEALTH OUTCOMES IN THE ADVANCE TRIAL**

**Evangelia E. Baxevanidi<sup>1</sup>**, Sumbul Asif<sup>2</sup>, Ambar Qavi<sup>1</sup>, Andrew Hill<sup>3</sup>, Francois Venter<sup>4</sup>, Fairlie Lee<sup>5</sup>, Masebole Masenya<sup>5</sup>, Celicia M. Serenata<sup>4</sup>, Simiso Sokhela<sup>4</sup>, Nomathemba Chandiwana<sup>4</sup>

<sup>1</sup>Imperial College London, London, UK, <sup>2</sup>University of Leeds, Leeds, UK, <sup>3</sup>University of Liverpool, Liverpool, UK, <sup>4</sup>Ezintsha, University of the Witwatersrand, Johannesburg, South Africa, <sup>5</sup>Wits RHI, University of the Witwatersrand, Johannesburg, South Africa

**Background:** First-line treatment with the integrase inhibitor dolutegravir (DTG) is associated with significant and progressive weight gain, especially among black women and if combined with TAF/FTC. If women become clinically obese after long-term treatment, this could increase risks of adverse birth and child health outcomes. This analysis assessed long-term risks of adverse outcomes in pregnancy and child health from treatment-associated clinical obesity among pregnant women, using data from the ADVANCE trial.

**Methods:** In the ADVANCE trial treatment-naïve patients were randomised to TAF/FTC+DTG, TDF/FTC+DTG or TDF/FTC/EFV for 144 weeks. A systematic review analysed the association between pre-pregnancy obesity and adverse maternal and infant outcomes. The association between pre-pregnancy obesity and adverse outcomes in child health (ages 6–16) was also measured. Risk ratios using the Mantel-Haenszel test with random-effects were calculated. Risk ratios of the pregnancy and child health outcomes were combined with treatment-associated obesity rates from ADVANCE to predict the number of women, infants and children who could experience adverse events in each arm at Week 144.

**Results:** After 144 weeks of treatment in the ADVANCE trial, the percentage of women with normal baseline BMI becoming clinically obese was 19% for TAF/FTC+DTG, 5% for TDF/FTC+DTG, and 0% for TDF/FTC/EFV. From baseline to Week 144, the predicted increase of adverse maternal outcomes was 15% with TAF/FTC+DTG versus 4% with TDF/FTC+DTG, whereas risk predictions for adverse infant outcomes were 12% and 3% in these two treatment groups. Similarly, the predicted risk of adverse outcomes in child health was 28% and 7% on TAF/FTC+DTG and TDF/FTC+DTG, respectively. No additional adverse events were predicted for pregnant women treated with TDF/FTC/EFV.

**Conclusion:** Pre-conception weight gain on antiretrovirals could substantially increase adverse outcomes in pregnancy and child health. There are consistent associations between pre-pregnancy clinical obesity and higher risks of adverse maternal, infant and child health outcomes. For every 100 women becoming pregnant after three years of TAF/FTC+DTG treatment, this analysis predicted 18 additional adverse outcomes. New stopping rules may be required to switch women off TAF/FTC+DTG and similar combination treatments, to lessen these risks.

Table 1: Predicted risk of adverse outcomes in pregnancy and child health among 100 pregnant women in the ADVANCE trial receiving ART for 144 weeks.

| Adverse outcomes  | Baseline | TAF/FTC+DTG |                 | TDF/FTC+DTG |                 | TDF/FTC/EFV |                 |
|---|----------|-------------|-----------------|-------------|-----------------|-------------|-----------------|
|   |          | Year 3      | Absolute change | Year 3      | Absolute change | Year 3      | Absolute change |
| Gestational hypertension  | 2.8      | 4.3         | +1.5            | 3.2         | +0.4            | 2.8         | +0              |
| Gestational diabetes  | 1.6      | 2.5         | +0.9            | 1.8         | +0.2            | 1.6         | +0              |
| Pre-eclampsia   | 2.5      | 3.9         | +1.4            | 2.8         | +0.3            | 2.5         | +0              |
| Postpartum haemorrhage  | 11.2     | 11.7        | +0.5            | 11.3        | +0.1            | 11.2        | +0              |
| Caesarean section   | 21.3     | 23.9        | +2.6            | 22.0        | +0.7            | 21.3        | +0              |
| Large-for-gestational-age   | 13.4     | 16.1        | +2.7            | 14.1        | +0.7            | 13.4        | +0              |
| Macrosomia  | 3.1      | 3.9         | +0.8            | 3.3         | +0.2            | 3.1         | +0              |
| Child overweight and obesity  | 7.2      | 11.0        | +3.8            | 8.2         | +1.0            | 7.2         | +0              |
| Child cardiometabolic risk factors (systolic blood pressure, triglycerides, insulin and C-peptide levels) | 4.1      | 5.3         | +1.2            | 4.4         | +0.3            | 4.1         | +0              |
| Child respiratory disorders (asthma)  | 11.0     | 12.4        | +1.4            | 11.4        | +0.4            | 11.0        | +0              |
| Child neurodevelopmental disorders  | 0.9      | 1.0         | +0.1            | 0.9         | +0              | 0.9         | +0              |

**573 ANTIRETROVIRAL THERAPY CLASS AND GESTATIONAL WEIGHT GAIN: RESULTS FROM PHACS SMARTT**

**Jennifer Jao<sup>1</sup>**, Carly Broadwell<sup>2</sup>, Paige L. Williams<sup>2</sup>, Ellen G. Chadwick<sup>1</sup>, Lisa Haddad<sup>2</sup>, Denise Jacobson<sup>2</sup>, Kathleen M. Powis<sup>4</sup>, Lynn M. Yee<sup>1</sup>, Deborah Kacanek<sup>2</sup>, for the Pediatric HIV/AIDS Cohort Study (PHACS)

<sup>1</sup>Northwestern University Feinberg School of Medicine, Chicago, IL, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Population Council, New York, NY, USA, <sup>4</sup>Massachusetts General Hospital, Boston, MA, USA

**Background:** Excessive gestational weight gain (GWG) is associated with poor maternal, perinatal, and metabolic outcomes. In non-pregnant persons living with HIV (PLHIV), integrase inhibitors (InSTIs) are associated with greater weight gain compared to protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

**Methods:** We evaluated the association of InSTI-based ART with GWG in pregnant PLHIV. The Surveillance Monitoring for ART Toxicities (SMARTT) study has enrolled pregnant PLHIV across 22 US sites since 2007. We analyzed GWG in pregnant PLHIV in SMARTT with available weight data, singleton gestations, and ART (consisting of ≥3 antiretrovirals) initiation at <16 wks gestational age (GA) from 2007–2019. GWG [(delivery weight) - (pre-pregnancy weight or weight taken at <12 wks GA)] was classified as excessive, adequate, or inadequate using National Academy of Medicine standards. ART was categorized as InSTI-based, PI-based, NNRTI-based, nucleoside reverse transcriptase (NRTI)-based, or ART consisting of ≥3 antiretroviral (ARV) classes which may have included an InSTI. Modified Poisson models were fit with generalized estimating equations

to assess the association of earliest ART class with prevalence of excessive (vs. adequate/inadequate) GWG. Pregnancies with ART use at conception (ART-C) and those with ART initiation in pregnancy (ART-I) were analyzed separately. Sensitivity analyses were performed with GWG modeled as excessive vs. adequate GWG.

**Results:** 1477 pregnancies (847 ART-C, 630 ART-I) of 1282 PLHIV were included. The prevalence of excessive, adequate, and inadequate GWG was 652 (44%), 350 (24%), and 475 (32%) respectively. Age (mean 29.3 years), earliest CD4 count (11% <200 cells/mm<sup>3</sup>) and viral load (60% < 400 copies/mL) in pregnancy, pre-gestational diabetes 3%, and GA at delivery (median 38 wks) were similar among GWG groups. No associations between ART class and excessive GWG were observed in ART-C or ART-I pregnancies after adjusting for age, race, ethnicity, income, earliest pregnancy viral load, and alcohol, tobacco, or substance use in pregnancy (Table). Results from sensitivity analyses were similar.

**Conclusion:** Initiation of INSTI-based ART prior to conception or before 16 wks GA was not associated with excessive GWG in pregnant PLHIV in the US. Future studies are needed to assess whether specific INSTIs or switching to an INSTI in pregnancy is associated with GWG.

Table. Unadjusted and adjusted estimates for the relative risk of excessive gestational weight gain vs. adequate/inadequate gestational weight gain by earliest class of ART in pregnancy, stratified by timing of ART initiation

| Timing of ART initiation                | Class of ART        | n     | Unadjusted    |              |                   | Adjusted*     |              |                   |
|---|---------------------|-------|---------------|--------------|-------------------|---------------|--------------|-------------------|
|   |                     |       | Relative Risk | 95% CI       | p-value           | Relative Risk | 95% CI       | p-value           |
| Using ART at conception <sup>†</sup>    | INSTI-based ART     | (169) | REF           | --           | 0.85 <sup>‡</sup> | REF           | --           | 0.93 <sup>‡</sup> |
|   | PI-based ART        | (428) | 1.05          | (0.85, 1.31) | 0.65              | 1.09          | (0.87, 1.36) | 0.45              |
|   | NNRTI-based ART     | (191) | 1.06          | (0.82, 1.36) | 0.67              | 1.09          | (0.85, 1.40) | 0.51              |
|   | NRTI-based ART      | (12)  | 1.21          | (0.88, 2.15) | 0.52              | 1.08          | (0.56, 1.98) | 0.88              |
|   | ≥ 3 classes of ARVs | (82)  | 1.23          | (0.86, 1.75) | 0.28              | 1.16          | (0.78, 1.71) | 0.44              |
| Initiated ART in pregnancy <sup>†</sup> | INSTI-based ART     | (88)  | REF           | --           | 0.67 <sup>‡</sup> | REF           | --           | 0.78 <sup>‡</sup> |
|   | PI-based ART        | (410) | 0.88          | (0.66, 1.08) | 0.20              | 0.90          | (0.72, 1.12) | 0.34              |
|   | NNRTI-based ART     | (79)  | 0.89          | (0.66, 1.22) | 0.48              | 0.88          | (0.65, 1.20) | 0.41              |
|   | NRTI-based ART      | (42)  | 0.78          | (0.50, 1.15) | 0.19              | 0.83          | (0.55, 1.26) | 0.39              |
|   | ≥ 3 classes of ARVs | (11)  | 1.03          | (0.60, 1.78) | 0.91              | 1.15          | (0.71, 1.88) | 0.56              |

\* Adjusted for racial self-identity (White, Black or African American, or other race), ethnic self-identity (Hispanic or Latina or not), age at delivery, annual household income (<\$10,000, \$10,000-\$30,000, >\$30,000, or unknown), earliest viral load in pregnancy (>400 copies/mL, vs. ≤400 copies/mL), alcohol or tobacco use in the first trimester, and other substance use in the first trimester. <sup>†</sup>INSTI = INSTI.

<sup>‡</sup>P-values on reference row indicate type III tests of significance for the association of earliest ART class with excessive GWG.

Estimates for relative risk of excessive gestational weight gain from modified Poisson models fit with GEE.

ART=antiretroviral therapy; ARV=antiretroviral; CI=confidence interval; INSTI=integrase strand transfer inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

to have higher triglyceride levels and GDM, but lower levels of TC and LDL cholesterol. These novel data indicate the burden of cardiometabolic risk factors in HIV+ pregnant women and point to the need to strengthen services to diagnose and manage cardiometabolic health in HIV+ women.

Table. Cardiometabolic health indicators at 24-28 weeks gestation among 231 pregnant women in Cape Town, South Africa, overall and by HIV status

|   | Total (n=231)     | HIV-uninfected (n=149) | Women living with HIV (n=82) | p-value <sup>1</sup> |
|---|-------------------|------------------------|------------------------------|----------------------|
| <b>Median, IQR</b>                      |                   |                        |                              |                      |
| Gestational age at first ANC            | 15 (11, 20)       | 15 (11, 20)            | 15 (11, 20)                  | 0.94                 |
| Parity                                  | 3 (2, 3)          | 2 (1, 3)               | 3 (2, 4)                     | <0.01                |
| Pre-pregnancy BMI (kg/m <sup>2</sup> )  | 30.5 (25.8, 35.8) | 31.0 (26.4, 35.9)      | 29.7 (25.7, 34.9)            | 0.21                 |
| <b>Plasma Glucose, mmol/l</b>           |                   |                        |                              |                      |
| Fasting                                 | 4.2 (3.9, 4.4)    | 4.1 (3.9, 4.3)         | 4.3 (4.1, 4.7)               | 0.05                 |
| 1-hour                                  | 6.1 (5.2, 6.9)    | 6.0 (5.1, 6.8)         | 6.2 (5.3, 7.1)               | 0.07                 |
| 2-hours                                 | 5.6 (4.8, 6.3)    | 5.6 (4.8, 6.4)         | 5.7 (5.0, 6.3)               | 0.25                 |
| <b>Lipids, mmol/l</b>                   |                   |                        |                              |                      |
| Total cholesterol                       | 4.7 (4.1, 5.4)    | 4.8 (4.2, 5.4)         | 4.5 (3.8, 5.0)               | 0.01                 |
| HDL cholesterol                         | 1.7 (1.4, 1.9)    | 1.7 (1.4, 1.9)         | 1.7 (1.5, 2.0)               | 0.34                 |
| LDL cholesterol                         | 2.3 (1.7, 2.7)    | 2.4 (1.9, 2.8)         | 1.9 (1.5, 2.5)               | <0.01                |
| Triglycerides                           | 1.5 (1.2, 1.9)    | 1.5 (1.2, 1.7)         | 1.6 (1.3, 2.0)               | 0.03                 |
| <b>Blood pressure, mm/Hg</b>            |                   |                        |                              |                      |
| Systolic                                | 112 (105, 120)    | 114 (107, 122)         | 109 (103, 117)               | <0.01                |
| Diastolic                               | 67 (63, 72)       | 67 (63, 72)            | 66 (63, 71)                  | 0.40                 |
| <b>N(%)</b>                             |                   |                        |                              |                      |
| Primigravida                            | 41 (18%)          | 38 (26%)               | 3 (4%)                       | <0.01                |
| <b>Pre-pregnancy BMI category</b>       |                   |                        |                              |                      |
| Underweight (BMI < 18.5)                | 0 (0%)            | 0 (0%)                 | 0 (0%)                       | 0.50                 |
| Normal weight (BMI 18.5-24.9)           | 41 (18%)          | 27 (18%)               | 14 (17%)                     |                      |
| Overweight (BMI 25-29.9)                | 65 (28%)          | 38 (26%)               | 27 (33%)                     |                      |
| Obese (BMI ≥30)                         | 124 (54%)         | 83 (56%)               | 41 (50%)                     |                      |
| <b>Hypertension<sup>2</sup></b>         |                   |                        |                              |                      |
| Systolic                                | 9 (4%)            | 7 (5%)                 | 2 (2%)                       | 0.39                 |
| <b>Gestational Diabetes<sup>3</sup></b> |                   |                        |                              |                      |
| Systolic                                | 9 (4%)            | 3 (2%)                 | 6 (7%)                       | 0.05                 |

<sup>1</sup>Using t-test of Mann-Whitney tests for continuous variables and Chi-square tests for categorical variables. <sup>2</sup>Defined as ≥130 systolic / ≥80 diastolic mm Hg. <sup>3</sup>Diagnosed via WHO guidelines: fasting plasma glucose ≥5.1 mmol/l, 1-hour plasma glucose ≥ 10.0 mmol/l or 2-hour plasma glucose ≥8.5 mmol/l.

## 575 TIMING OF ART INITIATION IS ASSOCIATED WITH HYPERTENSIVE DISORDERS OF PREGNANCY

Ellen G. Chadwick<sup>1</sup>, Denise Jacobson<sup>2</sup>, Lisa Haddad<sup>3</sup>, Jennifer Jao<sup>4</sup>, Kathleen M. Powis<sup>5</sup>, Deborah Kacanek<sup>2</sup>, Rebecca Zash<sup>5</sup>, Alexandra DiPerna<sup>6</sup>, Lynn M. Yee<sup>4</sup>, for the Pediatric HIV/AIDS Cohort Study

<sup>1</sup>Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Population Council, New York, NY, USA, <sup>4</sup>Northwestern University, Chicago, IL, USA, <sup>5</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>6</sup>Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA

**Background:** Contemporary cohorts of women living with HIV (WLHIV) appear to be at higher risk of development of hypertensive disorders of pregnancy (HDP) than those in the pre-antiretroviral therapy (ART) era. Whether due to rapid immune reconstitution with specific antiretroviral (ARV) classes when initiated during pregnancy, the ARVs themselves, or other risk factors is unclear. We examined the association of timing of ART initiation and ARV class with risk of new-onset HDP in pregnant WLHIV.

**Methods:** Data were abstracted from medical records of all pregnant WLHIV enrolled in the US-based multisite Surveillance Monitoring for ART Toxicities (SMARTT) study between 1/30/15 and 03/25/19. Pregnancies with multiple fetuses or no ART use were excluded. Hypertension (HTN) categories were classified by clinician diagnoses of HDP and/or timing of anti-HTN medications during pregnancy. New-onset HDP was defined as gestational HTN, preeclampsia (PE), or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets); individuals with chronic HTN were excluded from analysis of new-onset HDP. We examined the association of three exposures, each in a separate model, with relative risk of new-onset HDP compared to no HTN by fitting unadjusted and adjusted log-binomial regression models using generalized estimating equations to account for correlations within women with multiple singleton pregnancies. Exposures of interest were: timing of initial ART (preconception, <20 or ≥20 weeks' gestation) and ART class (PI, NNRTI, INSTI) at conception and initiated during pregnancy.

**Results:** 973/1038 pregnancies were singletons with complete data on HTN diagnosis; 948/973 WLHIV received ART during pregnancy (median age 28.9 years; 69% identified as Black, 25% as White, 26% as Hispanic ethnicity.) Overall, 9% of pregnancies had new-onset HDP, 10% had chronic HTN and 81% had no HTN. Relative risk of new-onset HDP did not differ by ART class, but those initiating ART after 20 weeks had a significantly increased risk of HDP (adjusted RR 1.94 95% CI 1.13-3.32) compared with those on ART at conception (see Table).

**Conclusion:** In this large, diverse cohort of WLHIV, 9% of pregnancies had new-onset HDP, with ART initiation at >20 weeks of gestation conferring higher risk, suggesting a potential role for rapid immune reconstitution later in pregnancy. However, in contrast to prior hypotheses, HDP was not associated with ARV class.

## 574 CARDIOMETABOLIC HEALTH IN HIV+ AND HIV- PREGNANT SOUTH AFRICAN WOMEN

Angela Bengtson<sup>1</sup>, Hlengiwe Madlala<sup>2</sup>, Zandile Maqwatini<sup>2</sup>, Azetta Fisher<sup>2</sup>, Landon Myer<sup>2</sup>

<sup>1</sup>Brown University, Providence, RI, USA, <sup>2</sup>University of Cape Town, Cape Town, South Africa

**Background:** HIV and antiretroviral therapy (ART) frequently influences cardiometabolic health, including obesity, glucose metabolism, lipids, and blood pressure (BP), but there are few data on the cardiometabolic impact of HIV and ART in pregnancy.

**Methods:** We consecutively enrolled HIV+ and HIV- women in routine antenatal care at 24-28 weeks' gestation in Cape Town. At enrollment, women underwent a fasted 2-hour oral glucose tolerance test for gestational diabetes (GDM), diagnosed via WHO guidelines (fasting plasma glucose (PG) ≥5.1 mmol/l, 1-hour PG ≥ 10.0 or 2-hour PG ≥8.5). Fasted blood samples were used to evaluate triglycerides, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. BP and anthropometry was assessed by trained research staff. Self-reported pre-pregnancy weight was used to estimate pre-pregnancy body mass index (BMI); obesity = pre-pregnancy BMI ≥ 30. Hypertension was defined as ≥130/80 mmHg. All HIV+ women were on TDF 300mg+3TC 300mg/FTC 200mg+EFV 600mg pre (n=76) or post (n=6) conception.

**Results:** Among 231 women (82 HIV+, 149 HIV-), the median gestational age at first antenatal care was 15 weeks (IQR 11, 20), 18% were primigravida (4% HIV+ vs 26% HIV-, p-value <0.01), and 54% were obese pre-pregnancy (HIV+ 50% vs HIV- 56%, p-value 0.50; Table). Systolic BP was higher among HIV- vs HIV+ women (114 vs 109, p-value <0.01) but the prevalence of hypertension was similar (5% vs 2%, p-value 0.39). Compared to HIV- women, HIV+ women had slightly higher median triglyceride levels (1.6 mmol/l vs 1.5, p-value 0.03), but lower TC (4.5 vs 4.8, p-value 0.01) and LDL cholesterol (1.9 vs 2.4, p-value <0.01) and similar HDL cholesterol (1.7 vs 1.7, p-value 0.34). HIV+ women had slightly higher fasting (4.3 mmol/l vs 4.1, p-value 0.05), 1-hour (6.2 vs 6.0, p-value 0.07), and 2-hour (5.7 vs 5.6, p-value 0.25) PG levels and GDM (7% vs 2%, p-value 0.05), compared to HIV- women. Adjusted for pre-pregnancy BMI and parity, HIV was marginally associated with GDM (RR 4.02, 95% CI 0.78-20.70, p-value 0.10).

**Conclusion:** In this cohort of pregnant HIV- and HIV+ women on EFV-based ART, over 50% were obese pre-pregnancy. HIV+ women were more likely

Table 1: Relative risk of new onset hypertensive disorders of pregnancy

| Exposure of interest              | Category Level of Exposure | N             |        | Unadjusted Relative Risk (95%CI) | Adjusted* Relative Risk (95%CI) |
|-----------------------------------|----------------------------|---------------|--------|----------------------------------|---------------------------------|
|                                   |                            | New onset HDP | No HTN |                                  |                                 |
| Timing of ART initiation          | Start ≥ 20 wks             | 18            | 92     | 1.91 (1.13, 3.22)                | 1.94 (1.13, 3.32)               |
|                                   | Start < 20 wks             | 34            | 278    | 1.27 (0.82, 1.98)                | 1.30 (0.83, 2.02)               |
|                                   | On ART at conception       | 37            | 395    | (ref)                            | (ref)                           |
| At Conception- ARV class          | PI based                   | 13            | 117    | 1.12 (0.56, 2.24)                | 1.11 (0.56, 2.22)               |
|                                   | NNRTI-based                | 7             | 109    | 0.68 (0.29, 1.59)                | 0.70 (0.30, 1.62)               |
|                                   | INSTI-based                | 16            | 163    | (ref)                            | (ref)                           |
| Initiating in pregnancy-ARV class | PI based                   | 21            | 138    | 0.98 (0.56, 1.69)                | 1.01 (0.58, 1.73)               |
|                                   | NNRTI-based                | 8             | 70     | 0.76 (0.36, 1.62)                | 0.79 (0.37, 1.66)               |
|                                   | INSTI-based                | 23            | 147    | (ref)                            | (ref)                           |

\*Adjusted for maternal age, maternal race/ethnicity, ARV timing also adjusted for high school education.

**576 THE RISK OF GESTATIONAL HYPERTENSION WITH USE OF DOLUTEGRAVIR AT CONCEPTION**

**Rebecca Zash**<sup>1</sup>, Ellen Caniglia<sup>2</sup>, Gloria Mayondi<sup>3</sup>, Modiegi Diseko<sup>3</sup>, Judith Mabuta<sup>3</sup>, Denise Jacobson<sup>4</sup>, Katherine Johnson<sup>5</sup>, Mompoti Mmalane<sup>3</sup>, Joseph Makhema<sup>3</sup>, Shahin Lockman<sup>6</sup>, Roger Shapiro<sup>4</sup>

<sup>1</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA, <sup>2</sup>New York University Langone Medical Center, New York, NY, USA, <sup>3</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>4</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>5</sup>University of Massachusetts, Worcester, MA, USA, <sup>6</sup>Brigham and Women's Hospital, Boston, MA, USA

**Background:** Hypertension (HTN) in pregnancy is an important cause of adverse maternal and fetal outcomes. Dolutegravir (DTG) has been associated with excess weight gain and adverse cardiometabolic effects in non-pregnant adults, which could lead to increased HTN during pregnancy. We therefore compared the risk of HTN in pregnancy among women on DTG to women on efavirenz (EFV), and to women without HIV (WVoH).

**Methods:** Tsepamo birth surveillance study data was used to emulate a hypothetical (target) trial where women would have been randomized to DTG- vs. EFV-based ART pre-conception and followed to delivery along with an observational arm of WVoH enrolled during pregnancy. The target trial included >18 y/olds who conceived 0.5-3 yrs after starting DTG- or EFV-based ART and delivered at one of the original 8 Tsepamo sites. WVoH were matched 2:1 to women with HIV by maternal age, gravida, site of delivery, and calendar yr of delivery. The primary outcome was gestational HTN, defined as onset of HTN (SBP >140 or DBP >90) after 20 weeks gestational age (GA) excluding those with chronic HTN. Secondary outcomes included women with chronic HTN and 1) any HTN (SBP >140 or DBP >90 at any GA), 2) severe HTN (SBP >160 or DBP >110 at any GA) and 3) early HTN (onset of hypertension before 34 wks GA). We fit multivariable log-binomial regression models to estimate the RR of each hypertensive outcome.

**Results:** Of 176,321 deliveries between Aug 2014-Oct 2020, 16,412 fit criteria for the target trial, including 2079 women conceiving on DTG, 3735 women conceiving on EFV and 10,598 WVoH. Women in the DTG and EFV groups were less likely to be married than WVoH (7.6% vs. 9.3% vs. 18.8%) while women on DTG and WVoH were more likely to be nulliparous than women on EFV (15.0% vs. 12.1% vs. 9.2%). Maternal age, history of chronic HTN, number of prenatal visits and GA at first blood pressure measurement were similar across arms. Gestational HTN occurred in 12.8% of women on DTG, 10.1% of women on EFV, and 14.7% among WVoH. Compared with DTG, the risk of gestational HTN was lower with EFV (aRR 0.79, 95% CI 0.68, 0.93) and higher among WVoH (1.17, 95% CI 1.03, 1.33). Any HTN, severe HTN and early HTN were also less common among EFV-conception and more common among women without HIV than DTG-conception (Table).

**Conclusion:** Gestational HTN is more common among women on DTG at conception than women on EFV at conception, but less common than in WVoH. Further research is needed to determine if this is related to maternal weight.

Table. Hypertensive Outcomes among women on DTG at conception, EFV at conception and Women Without HIV in a hypothetical (target) trial using observational data from the Tsepamo study in Botswana.

|                                       |                        | DTG at conception (N=2079) | EFV at conception (N=3735) | Women without HIV (N=10,598) |
|---------------------------------------|------------------------|----------------------------|----------------------------|------------------------------|
| <b>Gestational Hypertension</b>       | No. (%)                | 263 (12.8%)                | 373 (10.1%)                | 1525 (14.7%)                 |
|                                       | Unadjusted RR (95% CI) | ref                        | 0.79 (0.68,0.92)           | 1.15 (1.01,1.29)             |
|                                       | Adjusted RR* (95% CI)  | ref                        | 0.79 (0.68,0.93)           | 1.17 (1.03,1.33)             |
| <b>Any Hypertension</b>               | No. (%)                | 416 (20.0%)                | 572 (15.3%)                | 2413 (22.8%)                 |
|                                       | Unadjusted RR (95% CI) | ref                        | 0.77 (0.68,0.86)           | 1.15 (1.01,1.29)             |
|                                       | Adjusted RR* (95% CI)  | ref                        | 0.74 (0.65,0.84)           | 1.13 (1.03,1.25)             |
| <b>Severe Hypertension</b>            | No. (%)                | 27 (1.3%)                  | 40 (1.1%)                  | 205 (1.9%)                   |
|                                       | Unadjusted RR (95% CI) | ref                        | 0.82 (0.51,1.34)           | 1.49 (1.00,2.22)             |
|                                       | Adjusted RR* (95% CI)  | ref                        | 0.62 (0.37,1.04)           | 1.24 (0.82,1.88)             |
| <b>Early Gestational Hypertension</b> | No. (%)                | 154 (7.4%)                 | 250 (6.7%)                 | 950 (9.0%)                   |
|                                       | Unadjusted RR (95% CI) | ref                        | 0.90 (0.75,1.10)           | 1.21 (1.03,1.43)             |
|                                       | Adjusted RR* (95% CI)  | ref                        | 0.85 (0.68,1.04)           | 1.19 (0.999,1.42)            |

\* all models adjusted for maternal age, marital status, education, occupation, gravida, tertiary site of delivery, and calendar year of delivery.

**577 TRAJECTORIES OF PERINATAL DEPRESSION SYMPTOMS IN KENYAN WOMEN LIVING WITH HIV**

**Osborn Lusi**<sup>1</sup>, Anna Larsen<sup>2</sup>, Keshet Ronen<sup>2</sup>, Barbra A. Richardson<sup>2</sup>, Wenwen Jiang<sup>2</sup>, Bhavna Chohan<sup>3</sup>, Daniel Matemo<sup>1</sup>, Jennifer A. Unger<sup>2</sup>, Alison L. Drake<sup>2</sup>, John Kinuthia<sup>1</sup>, Grace John-Stewart<sup>2</sup>

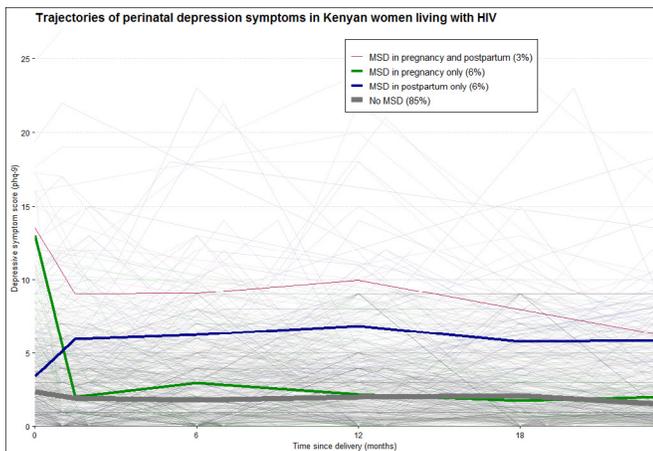
<sup>1</sup>Kenya National Hospital, Nairobi, Kenya, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>Kenya Medical Research Institute, Nairobi, Kenya

**Background:** Pregnant and postpartum (PP) women living with HIV (WLWH) experience elevated risk of depression. We examined longitudinal patterns and predictors of depressive symptoms among perinatal Kenyan WLWH who participated in a randomized trial of mHealth interventions.

**Methods:** We followed 824 WLWH enrolled in pregnancy through 24 months postpartum (PP) in 6 Nairobi and Nyanza region maternal child health (MCH) clinics. Study nurses assessed depressive symptoms during pregnancy, 6 weeks, 6, 12, 18, and 24 months PP using Patient Health Questionnaire-9 (PHQ-9). Psychosocial factors were evaluated using the: Stigma Scale for Chronic Illness, Medical Outcomes Study Social Support Survey, Abuse Assessment Screen for intimate partner violence (IPV), and Household Food Insecurity Access Scale. We evaluated prevalence of moderate-to-severe depressive symptoms (MSD; PHQ-9 score ≥10) and pre-defined symptom trajectories (no MSD ever, MSD in pregnancy only, PP MSD only, and MSD in pregnancy and PP). We identified correlates of any PP MSD using generalized estimating equations with Poisson link and independent correlation clustered by participant.

**Results:** During pregnancy, 8.6% (71/824) of WLWH had MSD; 9% (70/776) reported any PP MSD. Among WLWH with ≥1 PP visit, 85% (660/776) had no MSD in the perinatal period, 6% (46/776) had MSD in pregnancy only, 6% (49/776) had PP MSD only, 3% (21/776) had MSD during pregnancy and PP. Risk of any PP MSD was substantially higher among those with MSD in pregnancy (Relative Risk [RR]:5.9, 95% Confidence Interval [95% CI]:3.5-9.9), experiencing IPV ever (RR:2.9, 95% CI:1.7-4.9) and since the prior visit (RR:2.6, 95% CI:1.4-4.8), reporting stigma (RR:4.4, 95% CI:2.8-6.8), and with severe food insecurity (RR:3.4, 95% CI:2.2-5.2). Protective factors included HIV status disclosure to partner (RR:0.5, 95% CI:0.2-0.8) and higher social support (RR:0.97, 95% CI:0.96-0.98). Risk of MSD within 6 months PP was higher than >12 months PP (RR:1.8, 95% CI:1.1-2.8). Risk of any PP MSD did not differ by mHealth study arm. Results were similar in WLWH with PP MSD only.

**Conclusion:** About 16% of perinatal Kenyan WLWH attending public sector MCH services had MSD over a 2 year follow-up. Interventions to address depressive symptoms should be integrated into HIV/MCH services and prioritized for those reporting IPV, stigma, or food insecurity. Interventions that encourage disclosure of HIV status, reduce HIV-related stigma, and enhance social support may decrease MSD in this population.



### 578 ANTENATAL PROGESTERONE PROTECTS AGAINST FETAL GROWTH RESTRICTION IN WOMEN WITH HIV

**Madelyn Conner**<sup>1</sup>, Bellington Vwalika<sup>2</sup>, Stephen Cole<sup>1</sup>, Bethany Freeman<sup>1</sup>, Chileshe Mabula-Bwalya<sup>2</sup>, Marc Peterson<sup>1</sup>, Pooja Saha<sup>1</sup>, Elizabeth Stringer<sup>1</sup>, Margaret P. Kasaro<sup>3</sup>, Jeff Stringer<sup>1</sup>, Joan T. Price<sup>3</sup>

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>University of Zambia, Lusaka, Zambia, <sup>3</sup>University of North Carolina in Zambia, Lusaka, Zambia

**Background:** Widespread use of antiretroviral therapy (ART) has substantially reduced vertical HIV transmission. Second-line ART regimens that include protease inhibitors (PI) have been linked to adverse pregnancy outcomes such as maternal preeclampsia (PEC) and fetal growth restriction. Progesterone supplementation reverses PI-associated placental angiogenic changes in mouse models.

**Methods:** The Improving Pregnancy Outcomes with Progesterone (IPOP) trial was a phase III double-masked study that randomized pregnant women with HIV in Lusaka, Zambia to weekly injections of either 17 alpha-hydroxyprogesterone caproate (17P) or placebo starting at 16-24 weeks gestation. The trial's primary outcome, preterm birth <37 weeks or stillbirth at any gestational age, did not differ by randomization group. In a secondary analysis, we evaluated the risk of PEC and small for gestational age <3% (SGA3) associated with PI-based ART and evaluated whether 17P modified this risk.

**Results:** From Feb 2018 to Jan 2020, 800 pregnant women with HIV were randomized to either 17P (399) or placebo (401), of whom 24 (3%) were on a PI-based regimen; 11 randomized to 17P and 13 to placebo. Overall, 75 (9%) delivered an SGA3 infant, 5/24 (21%) on PI vs. 70/762 (9%) on non-PI regimens (RR 2.3; 95%CI 1.0, 5.1). Risk of SGA3 was 28/392 (7%) among those randomized to 17P compared to 47/394 (12%) randomized to placebo (RR 0.6; 95% CI 0.4, 0.9). In the placebo group, risk of SGA3 was higher among those on PIs (4/13; 31%) compared to those on other regimens (43/381; 11%) (RR 2.8; 1.2, 6.6), while the risk was similar in the 17P group (7.1% on PI vs. 9.0% non-PI) (RR 1.3; 0.2, 8.6). There were 15 (2%) preeclampsia events, 2/24 (8%) on PI vs. 13/776 (2%) on non-PI regimens (RR 5.0; 95%CI 1.2, 21.1). Risk of PEC was similar in 17P (9/401; 2%) compared to placebo groups (6/399; 2%) overall, although women randomized to placebo on PIs (2/13; 15%) compared to other regimens (7/388; 2%) had higher risk of PEC (RR 8.5; 95%CI 2.0, 37.1), while among those receiving placebo 0/11 on PIs compared to 6/388 (2%) of those on other regimens developed PEC.

**Conclusion:** Protease inhibitor use was associated with PEC and SGA. 17P was protective against SGA3 overall and may have modified the risk of both SGA3 and PEC in those with PI exposure. These findings suggest that progesterone may protect against placental vascular changes and the resultant adverse outcomes associated with PI-based therapy.

### 579 VAGINAL MICROBIOME AND INFLAMMATION PREDICT PRETERM BIRTH IN ZAMBIAN WOMEN WITH HIV

**Joan T. Price**<sup>1</sup>, Bellington Vwalika<sup>2</sup>, Michael France<sup>3</sup>, Humphrey Mwape<sup>4</sup>, Katelyn J. Rittenhouse<sup>1</sup>, Jacques Ravel<sup>3</sup>, Madelyn Conner<sup>1</sup>, Margaret P. Kasaro<sup>4</sup>, Kristina De Paris<sup>1</sup>, Jeff Stringer<sup>1</sup>

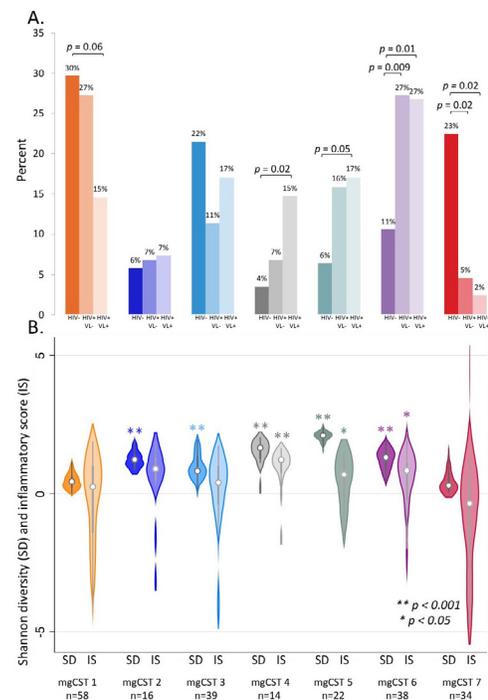
<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>University of Zambia, Lusaka, Zambia, <sup>3</sup>University of Maryland, Baltimore, MD, USA, <sup>4</sup>University of North Carolina in Zambia, Lusaka, Zambia

**Background:** Maternal HIV increases the risk of spontaneous preterm birth (sPTB). A Lactobacillus-deficient, anaerobe-dominant vaginal microbiome has been associated with sPTB, but few studies have assessed this association in the setting of HIV.

**Methods:** We performed a nested case-control study in a cohort of HIV-infected and uninfected women in Zambia who experienced either sPTB (case) or term birth (control). Vaginal swabs collected between 16-20 gestational weeks were used for whole metagenome sequencing of the vaginal microbiome and assays of 12 inflammatory markers. Assays were repeated at 24-36 weeks in the HIV-infected women. We used VIRGO, a non-redundant gene catalogues of the vaginal microbiome to group samples into 7 metagenomic community state types (mgCST) and created a vaginal inflammatory score for each corresponding sample with factor analysis.

**Results:** Of 221 participants, 29 (13%) had sPTB and 192 (87%) delivered at term. Median Shannon diversity index (SD) was highest in the 41 (19%) HIV-infected women with detectable plasma viral load (1.31, IQR: 0.85-1.66;  $p < 0.001$ ) and the 44 (20%) with undetectable virus (1.17, IQR: 0.51-1.66;  $p = 0.01$ ) vs. the 136 (62%) without HIV (0.74, IQR: 0.35-1.26). Inflammatory scores were positively correlated with SD (coeff +0.66, 95%CI 0.28, 1.03;  $p = 0.001$ ), and highest among the anaerobe-dominant mgCST2-mgCST6 (Fig 1A). HIV was associated with predominance of Gardnerella and mixed anaerobes in mgCST5 (17% vs. 6%;  $p = 0.02$ ) and mgCST6 (27% vs. 11%;  $p = 0.002$ ), and a lower prevalence of *L. crispatus*-dominant mgCST7 (4% vs. 23%;  $p = 0.001$ ) (Fig 1B). Relative abundance of Gardnerella above 1% (PR 2.8; 95%CI 1.4, 5.6), *L. iners* above 26% (PR 2.4; 95%CI: 1.21, 4.78), and *L. crispatus* below 0.02% (PR 4.4; 95%CI 1.08, 17.9) were each associated with sPTB. Vaginal inflammation at baseline (APR 2.8; 95%CI 1.5, 5.2) and, in the HIV-infected women, an increase in SD at repeat sampling (APR 2.5; 95%CI 1.1, 5.6) were associated with sPTB.

**Conclusion:** HIV in pregnancy is associated with a diverse, anaerobe-dominant vaginal microbiome, which in turn correlates with inflammation. Gardnerella and *L. iners* species predicted sPTB while *L. crispatus*, rare in women with HIV, was protective. These findings suggest the risk of PTB faced by women with HIV may be mediated by the vaginal microbial and inflammatory environment and could be a target for novel preventive therapies.



**580 PREGNANCY RATES & CLINICAL OUTCOME COMPARISONS AMONG WOMEN LIVING WITH HIV: HPTN 052**

**Sahar Z. Zangeneh**<sup>1</sup>, Ethan A. Wilson<sup>1</sup>, Surbahi Ahluwalia<sup>1</sup>, Deborah Donnell<sup>1</sup>, Ying Q. Chen<sup>1</sup>, Beatriz Grinsztajn<sup>2</sup>, Marineide G. Melo<sup>3</sup>, Sheela V. Godbole<sup>4</sup>, Mina C. Hosseinpour<sup>5</sup>, Taha E. Taha<sup>6</sup>, Johnstone Kumwenda<sup>7</sup>, Marybeth McCauley<sup>8</sup>, Myron S. Cohen<sup>5</sup>, Karin Nielsen-Saines<sup>9</sup>, for the HPTN 052 Study Team  
<sup>1</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>2</sup>Fiocruz, Manaus, Brazil, <sup>3</sup>Hospital Cristo Redentor, Porto Alegre, Brazil, <sup>4</sup>National AIDS Research Institute, Pune, India, <sup>5</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>6</sup>The Johns Hopkins University, Baltimore, MD, USA, <sup>7</sup>University of Malawi, Blantyre, Malawi, <sup>8</sup>FHI 360, Durham, NC, USA, <sup>9</sup>University of California Los Angeles, Los Angeles, CA, USA

**Background:** Early studies on the natural history of HIV infection in women suggest that untreated HIV infection is associated with reduction in fertility. HPTN 052 was one of few interventional clinical trials that allowed participation of pregnant women. We explored pregnancy and health characteristics in this cohort of women living with HIV.

**Methods:** HPTN 052 was a multi-country randomized trial evaluating the effect of early cART on sexual transmission of HIV among serodiscordant couples which allowed participation of pregnant women although contraception was recommended. Data on all HIV-infected index female participants was combined as a single longitudinal cohort. Cox proportional hazards models were used to infer associations between hypothesized static and time varying predictors and time to first pregnancy after study enrollment (Table). Analyses used SAS version 9.4.

**Results:** 869 women were followed for an average of 5.7 years (SD = 1.6). 115 women were pregnant at enrollment; 196 women had 1, 60 had 2 and 15 had > 3 pregnancies after enrollment; 532 women were never pregnant during the study. The mean time on ART was 4.61 years (SE = 0.09) for women ever pregnant (WEP) vs 4.67 years (SE=0.09) for women never pregnant (WNP). Annual pregnancy rate was 7.3% (362/4962 PY). AIDS was observed in 9.5% of WEP (32/337) vs 12.8% of WNP (68/532), p=0.17; STIs were present in 24% of WEP (80/337) vs. 22% of WNP (117/532), p=0.57. Partner seroconversion occurred in 8% of WEP (26/329) vs. 3.5% of WNP (18/517), p=0.008. In the multivariable model, CD4 cell count increases were associated with decreased pregnancy (adj HR=0.89 (0.84, 0.96)), but not virus load suppression (adj HR=1.01 (0.74,1.38)). Younger women and those in countries with lower contraceptive coverage had higher pregnancy rates. Partner seroconversion (as a surrogate for unprotected sex) was associated with higher pregnancy rates in univariate but not multivariable model; parity was associated with lower pregnancy rates in the univariate but not multivariable model; self-reported condom use was not associated with pregnancy (Table). Women on PI-based ART had higher pregnancy rates, likely due to study treatment guidelines.

**Conclusion:** Clinical outcomes were similar between ever pregnant/ never pregnant women. CD4 cell increase over time and parity were associated with reduced pregnancy suggesting that access to cART and contraceptives empowered women living with HIV in making family planning decisions.

**581 INCREASED C-SECTIONS AND PRETERM BIRTHS IN SARS-CoV-2 INFECTION DURING PREGNANCY**

**Itziar Carrasco**<sup>1</sup>, Mar Muñoz-Chapulí<sup>1</sup>, Sara Vigil-Vazquez<sup>1</sup>, David Aguilera-Alonso<sup>1</sup>, Concepción Hernández<sup>1</sup>, Monica Riaza<sup>2</sup>, Marta Pareja<sup>3</sup>, Olga Sanz<sup>4</sup>, Beatriz Pérez-Seoane<sup>5</sup>, Juan Lopez<sup>6</sup>, Elena Márquez<sup>7</sup>, Sara Domínguez-Rodríguez<sup>8</sup>, Juan Antonio De León Luis<sup>1</sup>, Manuel Sánchez-Luna<sup>1</sup>, María Luisa Navarro<sup>1</sup>  
<sup>1</sup>Hospital General Universitario Gregorio Marañón, Madrid, Spain, <sup>2</sup>Hospital Universitario HM Montepíncipe, Madrid, Spain, <sup>3</sup>Complejo Hospitalario Universitario de Albacete, Albacete, Spain, <sup>4</sup>Complejo Hospitalario de Navarra, Pamplona, Spain, <sup>5</sup>Hospital Universitario Infanta Sofía, Madrid, Spain, <sup>6</sup>Hospital Universitario Infanta Leonor, Madrid, Spain, <sup>7</sup>Hospital San Pedro de Alcántara, Cáceres, Spain, <sup>8</sup>Fundación Investigación Biomédica del Hospital 12 de Octubre, Madrid, Spain

**Background:** SARS-CoV2 infection severity during pregnancy and possible consequences for exposed newborns information is still unknown. The objective of this study is to analyse clinical and epidemiological characteristics of a SARS-CoV2 infected women during pregnancy and their newborns cohort.

**Methods:** Multicentric observational study from the Spanish GENE-COVID cohort (participating in RECLIP). Infected pregnant women and their newborns born from 15 March to 31 July with a 15 days follow up were included. Data regarding epidemiological, clinical, virological and immunological characteristics of the patients was collected.

**Results:** Globally, 105 pregnant women with a median age of 34 (IQR: 29 – 37) years old and 107 newborns were included in the study. Median gestational age at diagnosis was 36.9 (IQR\_ 33.4-39.2) weeks, and 6.7% of women were diagnosed in the second trimester. More than 34% of the women presented at least one comorbidity and almost 65% of women had COVID19 symptoms and 43% of them were treated for the infection. Overall, 30.8% had COVID-19 pneumonia and 4.8% were admitted to the intensive care unit (ICU) needing invasive mechanical ventilation. The rate of positive RT-PCR at delivery was 61.9%. There was a 36.2% rate of caesarean sections, associated with pneumonia during pregnancy OR:4.2 (95% CI 1.5,12.0) and lower gestational age at delivery OR:0.7 (95% CI: 0.6,0.9). Regarding newborns, 46.7% were male, 66.4% breastfed, with median Apgar 1' of 9 and Apgar 5' of 10. Almost 6% were small for gestational age and 16.8% needed admission to the neonatal ICU. Oxygen was needed by 12.1% and surfactant by 5.6% newborns. Prematurity rate was 20.6%, associated with pneumonia during gestation OR:7.0 (95% CI: 2.3,22.8) and with a positive RT-PCR at delivery OR:6.5 (95% CI: 1.8,31.8). No associations were found with age, comorbidities or blood group. No vertical transmission was reported but one newborn was horizontally infected. Two newborns died, one due to prematurity causes and another of unexpected sudden death during early skin-to-skin contact after delivery.

**Conclusion:** Even there is no vertical transmission reported in this cohort, we found a case of horizontal transmission. SARS-CoV2 infection could produce COVID19 pneumonia during pregnancy, that increases caesarean sections and prematurity rates worsening exposed newborns prognosis.

**582 PREGNANCY OUTCOMES OF WOMEN POSITIVE FOR SARS-CoV-2 COMPARED TO WOMEN TESTED NEGATIVE**

**Jeremie Mattern**<sup>1</sup>, Alexandre J. Vivanti<sup>1</sup>, Christelle Vauloup-Fellous<sup>1</sup>, Luce Landraud<sup>2</sup>, Laurent Mandelbrot<sup>2</sup>, Alexandra Benachi<sup>3</sup>, Olivier Picone<sup>2</sup>, Jeanne Sibude<sup>1</sup>  
<sup>1</sup>Assistance Publique-Hôpitaux de Paris, Paris, France, <sup>2</sup>Université de Paris, PARIS, France, <sup>3</sup>Université Paris-Saclay, Orsay, France

**Background:** Potential effects of infection with SARS-CoV-2 in pregnant women are still conflicted. Initial symptoms for COVID-19 are often unspecific, it is thus clinically relevant to know if a positive naso-pharyngeal real time reverse transcription PCR (RT-PCR) for SARS-CoV-2 at evaluation is predictive of perinatal outcomes. Our objective was to determine the impact of SARS-CoV-2 infection among women presenting with symptoms indicating a virological test.

**Methods:** We conducted a retrospective study including all pregnant women tested for SARS-CoV-2 by RT-PCR in respiratory tract samples from March 12-May 1st in two tertiary referral obstetric units in the Paris metropolitan area. Indication for tests were one or more of the following symptoms: fever (>38°C), coughing, dyspnea, anosmia, myalgia, rhinorrhea, nausea and vomiting or diarrhea. Clinical and biological characteristics at initial evaluation and perinatal outcomes were compared with student test Chi2 or Fisher tests as appropriate.

**Results:** 123 patients were tested for SARS-CoV-2, 55 were positive (45%). Pregnancy outcomes were available for 93% (N=114). Mean gestational

Table. Predictors of Pregnancy Among HIV+ Women following enrollment into HPTN 052. Results from Cox Proportional Hazards models.

| Variable  |                      | Univariable analysis     | Multivariable Analysis   |
|---|----------------------|--------------------------|--------------------------|
|   |                      | HR (95% C.I.)            | HR (95% C.I.)            |
| CD4 count (per 100 cells/mm3 increase)            |                      | <b>0.92 (0.87, 0.98)</b> | <b>0.89 (0.84, 0.96)</b> |
| Condom use at last sex (past 3 mo) (ref. = no)    | yes                  | 1.07 (0.75, 1.52)        | 1.06 (0.73, 1.54)        |
| Baseline ART regimen (ref. = NNRTI based regimen) | Did not initiate ART | 1.15 (0.51, 2.60)        | 0.56 (0.20, 1.51)        |
|   | PI based regimen     | <b>2.19 (1.72, 2.79)</b> | <b>2.25 (1.74, 2.91)</b> |
| HIV RNA <= 400 copies/mL (ref. = no)              | yes                  | 0.79 (0.61, 1.03)        | 1.01 (0.74, 1.38)        |
| Contraceptive coverage (ref. = 50-70%)            | >70% coverage        | <b>0.29 (0.20, 0.42)</b> | <b>0.28 (0.19, 0.42)</b> |
| Married/cohabitating (ref. = no)                  | yes                  | 1.35 (0.74, 2.47)        | 1.07 (0.54, 2.10)        |
| Parity (ref. = 0-1)                               | 2+                   | <b>0.72 (0.53, 0.97)</b> | 0.82 (0.60, 1.13)        |
| Age (cat.) (ref. = 18-24)                         | 25-34                | <b>0.60 (0.44, 0.82)</b> | <b>0.48 (0.34, 0.68)</b> |
|   | 35+                  | <b>0.14 (0.09, 0.22)</b> | <b>0.13 (0.08, 0.21)</b> |
| Partner seroconversion during study (ref. = no)   | yes                  | <b>2.02 (1.32, 3.07)</b> | 1.56 (1.00, 2.43)        |

age at testing was similar between the groups (29.2 vs 30.1WG,  $p=0.53$ ). The symptoms which were more frequent in women with positive PCR were anosmia: 22% (12/55) vs 9% (6/68),  $p=0.05$ , and myalgia: 33% vs 17%,  $p=0.04$ . Concerning biological characteristics, women with positive PCR were more often of blood type A (vs type O;  $p=0.004$ ), more often lymphopenic (47% vs 5%,  $p<0.001$ ), there was a trend towards more abnormal aPTT ratio ( $>1.2$ ) ( $p=0.07$ ). Hospitalization rates were higher for women tested positive: 41.8% vs 21.5%,  $p=0.02$ . All 8 women hospitalized in intensive unit care were tested positive. Preterm birth ( $<37$ WG) was higher in the group of women tested positive (30.2 vs 13.3%,  $p=0.029$ ) and there was a similar trend for severe preterm ( $<32$ WG) birth (15.1% vs 5.0%,  $p=0.07$ ). Among the 78 women not delivered 15 days after the test, the rate of preterm birth was similar in both groups: 17.1% (6/35) vs 11.6% (5/43),  $p=0.47$ . We found no difference in the rate of preeclampsia (4% vs 5%) or post-partum hemorrhage (15.1% vs 9.8%,  $p=0.41$ ). Birthweight Z-score did not differ between the groups ( $-0.3$  vs  $-0.1$ ,  $p=0.32$ ).

**Conclusion:** In a symptomatic pregnant population tested positive for SARS-CoV-2 compared to negative patients with same characteristics, COVID-19 infection seemed to increase medically indicated preterm births, especially during the 15 days after the RT-PCR result.

### 583 COMPROMISED SARS-CoV-2 NEUTRALIZING ANTIBODY RESPONSE IN CORD BLOOD VERSUS MOTHERS



**Sakthivel Govindaraj**<sup>1</sup>, Hongmei Gao<sup>2</sup>, Verkerke Hans<sup>1</sup>, Narayana Cheerdarla<sup>1</sup>, Les'Shon s. Irby<sup>1</sup>, Sindhu Potlapalli<sup>1</sup>, Daniel Endress<sup>1</sup>, Nanda K. Routhu<sup>1</sup>, Venkata S. Bollimpelli<sup>1</sup>, Chris Ibegbu<sup>1</sup>, Andrew S. Neish<sup>1</sup>, David Montefiori<sup>2</sup>, Rama R. Amara<sup>1</sup>, Alicia K. Smith<sup>1</sup>, Vijayakumar Velu<sup>1</sup>

<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Duke University, Durham, NC, USA

**Background:** Maternal antibodies are important for infant immunity, and understanding the maternal and umbilical cord antibody response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection will be important for neonatal management and maternal vaccination strategies.

**Methods:** The dynamics of maternal/ umbilical cord antibody responses to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein were analyzed in 81 samples from 69 pregnant women studied between April 2020 and January 2021. Binding IgG, IgA and IgM antibodies to RBD were measured by enzyme-linked immunosorbent assay (ELISA) in both maternal and cord blood. Neutralization was assessed using codon-optimized full-length G614 Spike-pseudotyped virus (VRC7480.D614G).

**Results:** Among the 69 pregnant women, 57 were either symptomatic or asymptomatic infection and 17 samples were taken during the time of delivery resulting in paired maternal/umbilical cord blood samples. Among the maternal samples tested, the RBD specific IgG were detected in 93%, IgA were detected in 67% and IgM were detected in 79%. The RBD-specific IgG was detected in 12 of 17 (70%) umbilical cord blood, but IgM and IgA were not detected in the cord blood samples. The IgG antibody concentration were significantly ( $P < 0.004$ ) lower (7 fold) in the cord blood when compared to maternal blood. However, the cord blood IgG titers were positively correlated with maternal IgG titers ( $r = 0.59$ ;  $P < 0.003$ ). In line with that, the circulating T- follicular helper cells ( $p < 0.0001$ ) and signaling lymphocytic activation molecule family 1 (SLAMF1) were lower ( $p < 0.004$ ) in cord relative to maternal blood. Among the samples tested, 71.4% had neutralization titers. Interestingly, the neutralization capacity of plasma from cord blood was negative when compared to maternal blood (mean titer of 20 vs 2128 respectively), suggesting that cord blood does not have capacity to neutralize the SARS-CoV-2 virus.

**Conclusion:** In this cohort study, maternal IgG, IgA and IgM antibodies to RBD of SARS-CoV-2 were seen in maternal samples. However the cord blood IgG levels were significantly lower and did not show positive titers for IgA and IgM. Although both maternal and cord blood has RBD binding antibodies, there is no neutralization seen in any of the cord blood tested compared to respective maternal blood. Our findings demonstrate that maternally-derived SARS-CoV-2 specific antibodies lack neutralization potential to provide neonatal protection from COVID-19.

### 584 THE ANTIRETROVIRAL PREGNANCY REGISTRY: 30 YEARS OF MONITORING FOR CONGENITAL ANOMALIES

**Jessica D. Albano**<sup>1</sup>, William R. Short<sup>2</sup>, Angela E. Scheuerle<sup>3</sup>, Karen Beckerman<sup>4</sup>, Lynne Mofenson<sup>5</sup>, Vani Vannappagari<sup>6</sup>

<sup>1</sup>Syneos Health, Wilmington, NC, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>University of Texas Southwestern, Dallas, TX, USA, <sup>4</sup>Icahn School of Medicine at Mt Sinai, New York, NY, USA, <sup>5</sup>Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, <sup>6</sup>ViiV Healthcare, Research Triangle Park, NC, USA

**Background:** Antiretrovirals (ARVs) effectively reduce perinatal transmission of HIV. The Antiretroviral Pregnancy Registry (APR) began monitoring prenatal ARV use in 1989 to provide an early signal of teratogenicity and to estimate the prevalence of congenital anomalies (CAs) which could be compared to the general population.

**Methods:** The APR is a prospective exposure-registration cohort study with data from 70 countries. Prevalence of CAs are estimated and compared to internal and external comparison groups. Twenty-two ARVs have sufficient 1st trimester exposures to detect at least a 2-fold increase in risk of CAs overall, of which 11 can detect a 1.5-fold increase.

**Results:** Of the 21,599 evaluable pregnancies enrolled through 31 July 2020, there were 20,437 live births (LB) with ARV exposure at any time during pregnancy and 580 CAs. Prevalence of CAs was 2.8% (95% CI 2.6-3.1) overall, 2.8% (95% CI 2.5-3.2) among 1st trimester ARV exposures and 2.8% (95% CI 2.5-3.2) among 2nd/3rd trimester ARV exposures to ARVs. Prevalence Ratio comparing 1st vs 2nd/3rd trimester ARV exposures was 1.00 (95% CI 0.85-1.17). Two ARVs, didanosine (DDI) and nelfinavir (NFV) have a modest statistically significant increase in overall prevalence compared to Metropolitan Atlanta Congenital Defects Program (MACDP) but not Texas Birth Defects Registry (TBDR); lower bound of the confidence interval for DDI (2.9%) and NFV (2.9%) is slightly above the higher bound for the comparator MACDP rate. Having reached the threshold of 200 first trimester exposed cases, the prevalence of CAs for tenofovir alafenamide (TAF) is 4.4% (95% CI 2.7-6.8). However, the lower end of the 95% CI is within the upper bound of the 95% CI for both the MACDP and the TBDR.

**Conclusion:** The APR has not found a significant difference in CA prevalence overall or by trimester of exposure compared to two population based surveillance systems: 2.72/100 LB (95% CI 2.68-2.76) MACDP and 4.17/100 LB (95% CI 4.15-4.19) TBDR. A detailed review of cases for DDI, NFV, or TAF did not identify a pattern of CAs. The clinical relevance of the statistical findings for DDI and NFV are unclear. Monitoring will continue. The APR independent Advisory Committee concludes, "The Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause; however, potential limitations of registries should be recognized".

### 585 NATIONAL EVALUATION OF MALAWI'S PMTCT PROGRAM: 24-MONTH HIV-EXPOSED INFANT OUTCOMES

**Monique Van Lettow**<sup>1</sup>, Joep J. Van Oosterhout<sup>1</sup>, Erik Schouten<sup>2</sup>, Andreas Jahn<sup>3</sup>, Thokozani Kalua<sup>4</sup>, Rose Nyirenda<sup>4</sup>, Megan Landes<sup>5</sup>

<sup>1</sup>Dignitas International, Zomba, Malawi, <sup>2</sup>Management Sciences for Health, Lilongwe, Malawi, <sup>3</sup>Government of Malawi Ministry of Health, Lilongwe, Malawi, <sup>4</sup>Malawi Department of HIV and AIDS, Lilongwe, Malawi, <sup>5</sup>University of Toronto, Toronto, Canada

**Background:** Data on long-term HIV-free survival in breastfeeding HIV-exposed infants (HEI) is limited. The National Evaluation of the Malawi Prevention of Mother-to-Child Transmission of HIV (PMTCT) Program (NEMAPP), conducted between 2014 and 2018, evaluated mother-to-child transmission (MTCT) and infant outcomes up to 24 months postpartum.

**Methods:** We enrolled a nationally representative cohort of HEI at 54 health facilities across 4 regional strata in Malawi and used multivariable cox regression analysis to investigate risk of adverse outcomes (HIV transmission, infant death and lost to follow-up) to 24 months postpartum. Models were fitted for the total cohort ( $n=3462$ ) and for a sub-cohort that received maternal viral load (VL) monitoring ( $n=1282$ ). Analyses were weighted to control for survey design.

**Results:** Of 3462 HEI, cumulative MTCT by 24 months was 4.9% (95% confidence intervals [CI] 3.7-6.4), 1.3% (95%CI 0.8-2.2) HEI had died, 26.2% (95%CI 24.0-28.6) were lost-to follow and 67.5% (95%CI 65.0-70.0) were alive and HIV-free. Of all mothers, 22.9% (95%CI 20.7-25.2) were young (14-24 years), 8.9% (95%CI

7.6-10.5) were primipara. 47.1% (95%CI 44.4- 49.9) had started antiretroviral therapy (ART) pre-conception, 50.5% (95%CI 47.7-53.2) post-conception and for 2.4% (95%CI 1.6-3.6) ART start was unknown. Of the sub-cohort of mothers, 83.8% (95%CI 81.1-86.2) had suppressed VL (<1,000 copies/mL) at enrolment. Parity (primipara: adjusted hazard ratio [aHR] 1.6, 95%CI 1.1-2.2; parity 2-3: aHR 1.5, 95%CI 1.2-1.9), mother-partner disclosure status (no disclosure: aHR 1.3, 95%CI 1.1-1.6; no partner: aHR 0.7, 95%CI 0.5-0.9), unknown maternal ART start (aHR 2.0, 95%CI 1.0-3.9) and poor adherence (missed >2 days of ART in the last month: aHR 1.7, 95%CI 1.2-2.2; not on ART: aHR 1.7, 95%CI 1.0-2.7) were associated with adverse outcomes to 24 months. In sub-cohort analysis, risk of HIV-transmission or infant death was higher among HEI whose mothers started ART post-conception (during pregnancy: aHR 3.2, 95%CI 1.3-7.7; postpartum aHR 12.4, 95%CI 1.5-99.6) or when maternal VL at enrolment was >1,000 copies/mL (aHR 15.7, 95%CI 7.8-31.3).

**Conclusion:** Infant positivity and infant mortality at 24 months were low for a breastfeeding population. Starting ART preconception had the highest impact on HIV-free survival in HEI. Further population-level reductions in MTCT may require additional interventions during breastfeeding for women new to PMTCT programs.

## 586 PREVENTING VERTICAL HIV TRANSMISSION IN THE UK: SUCCESSES AND EMERGING CHALLENGES

Helen Peters<sup>1</sup>, Kate Francis<sup>1</sup>, Laurette Bukasa<sup>1</sup>, Rebecca Sconza<sup>1</sup>, Laura Smeaton<sup>2</sup>, Sharon Webb<sup>2</sup>, Claire Thorne<sup>1</sup>

<sup>1</sup>UCL Great Ormond Street Institute of Child Health, London, UK, <sup>2</sup>Public Health England, London, UK

**Background:** The UK has met 90-90-90 targets since 2017 and a major success has been the low vertical HIV transmission rate (VTR), declining from 2.1% in 2000-01 to 0.28% in 2015-16 among diagnosed women living with HIV (WLHIV). The British HIV Association (BHIVA) recommends follow-up of all infants of WLHIV at 18-24mths ('18-24Ab'), regardless of negative PCR testing, to establish infection status and formula feeding to eliminate postnatal transmission risk. BHIVA guidelines state that virologically suppressed women on antiretroviral therapy (ART) with good adherence who choose to breastfeed may be clinically supported to do so.

**Methods:** The Integrated Screening Outcomes Surveillance Service (ISOSS), part of Public Health England's Infectious Diseases in Pregnancy Screening (IDPS) Programme, monitors all pregnancies to diagnosed WLHIV and their infants in the UK. All children diagnosed with HIV <16yrs are reported to ISOSS, with enhanced data collection for those vertically infected in the UK. Clinical Expert Review Panels establish circumstances surrounding transmissions and contributing factors. We describe maternal characteristics and VTRs among singleton liveborn infants in 2017-18 with HIV status reported by 30/09/20 and cases of supported breastfeeding since 2012.

**Results:** There were 1527 livebirths, with 89% (1353/1520) of mothers diagnosed pre-pregnancy, 77% (1141/1478) conceiving on ART and 93% (982/1053) with viral load (VL) <50c/ml at ≤30 days pre-delivery. To date, 88% (1337) of infants were classified uninfected based on ≥2 negative PCRs >1mth of age. 59% (784/1337) of infants were reported as uninfected based on 18-24Ab; 11% (145) were LTFU <18-24Ab, 12% (158) were discharged early based on a negative antibody between 3-17mths and 18% (250) infants only had negative PCRs reported. The 2017-18 VTR was 0.22% [95%CI 0.05, 0.65], with 3 transmissions where disengagement and late booking were factors. Where delivery VL was <50c/ml, the VTR was 0.11% ([95%CI 0.002, 0.64], 1/870). There have been 151 reports of supported breastfeeding among women on fully suppressive therapy since 2012 (duration: 1 day-24mths); of the 55 born 2017-18, infection status is unconfirmed in most cases and 6 infants were LTFU with unknown status.

**Conclusion:** The sustained low VTR reflects ongoing successes in pregnancy screening and clinical management. Increasing complexities of infant follow-up to 18-24mths, including LTFU in the supported breastfeeding era underscores the need for robust surveillance.

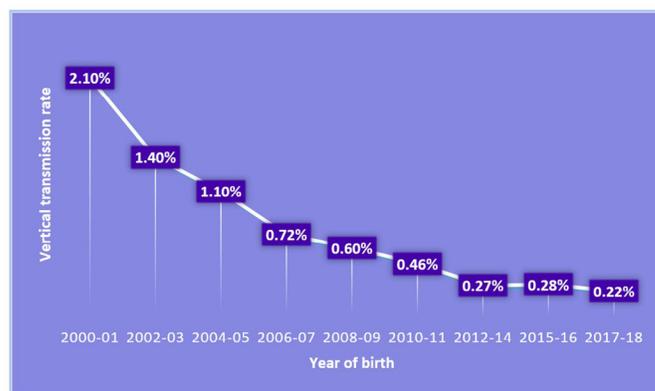


Figure: Vertical transmission rates of HIV among diagnosed women in the UK 2000-18

## 587 PRETERM BIRTH, BREASTFEEDING, ANTENATAL ARV REGIMEN, AND 24-MONTH HIV-FREE SURVIVAL

Mary G. Fowler<sup>1</sup>, Mauricio Pinilla<sup>2</sup>, Sufia Dadabhai<sup>3</sup>, Maxensia Owor<sup>4</sup>, Lynda Stranix-Chibanda<sup>5</sup>, Patricia Flynn<sup>6</sup>, Taha E. Taha<sup>3</sup>, Lameck Chinula<sup>7</sup>, Avy Violari<sup>8</sup>, Dhaya Moodley<sup>9</sup>, Katie McCarthy<sup>10</sup>, Renee Browning<sup>11</sup>, Sean Brummel<sup>2</sup>, Lynne Mofenson<sup>12</sup>, for the IMPAACT 1077 "PROMISE" Team

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>4</sup>Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda, <sup>5</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>6</sup>St Jude Children's Research Hospital, Memphis, TN, USA, <sup>7</sup>University of North Carolina Project-Malawi, Lilongwe, Malawi, <sup>8</sup>Perinatal HIV Research Unit, Soweto, South Africa, <sup>9</sup>University of KwaZulu-Natal, Durban, South Africa, <sup>10</sup>FHI 360, Durham, NC, USA, <sup>11</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, <sup>12</sup>Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA

**Background:** PROMISE 1077BF/1077FF was a multi-site, randomized, open-label, perinatal trial comparing the relative safety/efficacy of proven ARV regimens during pregnancy and breastfeeding (BF) among HIV+ women not meeting treatment criteria at trial entry. Previous results found <1% HIV transmission risk but increased risk of adverse pregnancy outcomes including preterm (PT, <37 weeks) delivery for mothers receiving antenatal triple ARVs (ART) compared to zidovudine (ZDV) alone. This raised concerns that antenatal ART and associated PT risk might impact later child survival.

**Methods:** In period I, pregnant HBV-/HIV+ women were randomized 1:1 to ZDV alone or ZDV/3TC/lopinavir-ritonavir (ZDV-ART) while HBV+/HIV+ women were randomized 1:1:1 to ZDV alone, ZDV-ART or tenofovir/emtricitabine/lopinavir-ritonavir (TDF-ART). In period II, enrollees were randomized 1:1:1 to the 3 regimens. We analyzed overall and HIV-free survival at 24-months for liveborn infants, based on (1) gestational age at delivery: PT (<37 weeks) or term (≥37 weeks) and (2) maternal antepartum ARV randomization. Kaplan-Meier method was used to calculate survival probabilities and 95% confidence intervals (CIs). Cox proportional hazards regression with BF (with ARVs) as a time-varying covariate was used to calculate hazard ratios (HR) and 95% CIs.

**Results:** For periods I-II there were no significant differences in 24 month HIV free survival between antenatal ZDV-ART or ZDV-alone regimens, but time-varying BF was associated with decreased risk of HIV infection or death (adjusted HR 0.14 (95%CI: 0.09-0.20)). In period II only, TDF-ART had >2-fold increased risk of HIV or death by 24 months compared to ZDV-ART (HR 2.37, 95%CI: 1.21-4.64); time-varying BF was associated with decreased risk of HIV or death (HR 0.05 (95%CI: 0.03-0.08)). In both periods, among 3482 liveborn infants (51% male; 97% African), there were 64 (2.2%) deaths and 53 (1.8%) HIV infections among 2914 term infants; and 62 (10.9%) deaths and 18 (3.2%) HIV infections among 568 PT infants (Figure). PT birth was associated with decreased 24-month HIV free survival: 0.85 (95%CI: 0.82-0.88) vs term birth: 0.96 (95%CI: 0.95-0.96); and 79% of PT deaths were neonatal (age < 30 days).

**Conclusion:** In PROMISE, PT birth <37 weeks was significantly associated with lower 24 month HIV-free survival, while BF was associated with increased HIV-free survival. Finding Interventions to decrease risk of PT birth for HIV+ mothers and prevent related infant deaths remain a high priority.

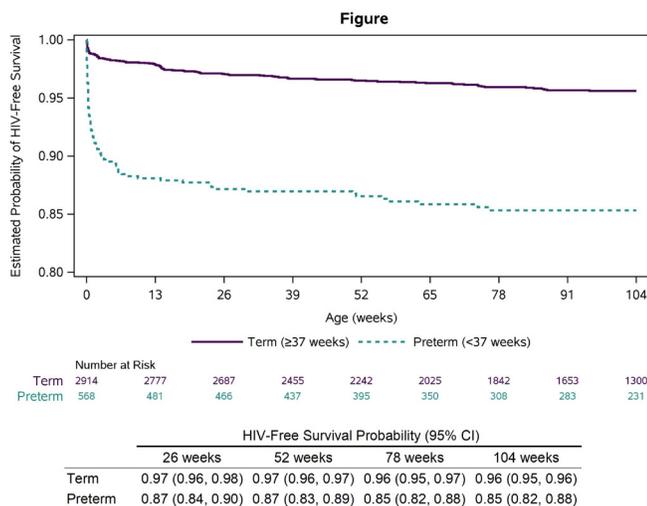
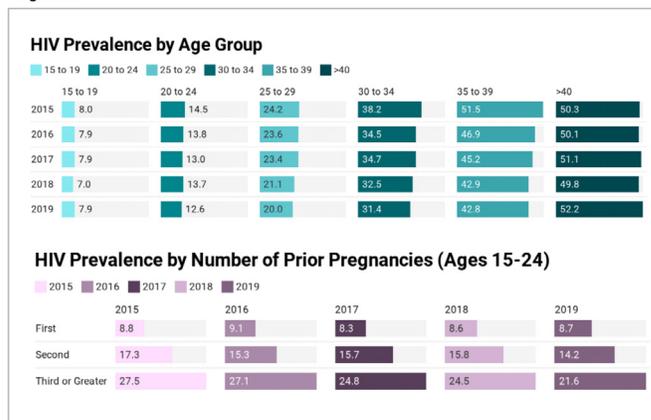


Figure 1



588 TRENDS IN HIV PREVALENCE AMONG PREGNANT WOMEN IN BOTSWANA: AN OPPORTUNITY FOR PrEP?

**Andrew Kapoor**<sup>1</sup>, Aamirah Mussa<sup>2</sup>, Modiegi Diseko<sup>2</sup>, Gloria Mayondi<sup>2</sup>, Judith Mabuta<sup>2</sup>, Mompoti Mmalane<sup>2</sup>, Joseph Makhema<sup>2</sup>, Chelsea Morroni<sup>3</sup>, Rebecca Zash<sup>1</sup>, Roger Shapiro<sup>1</sup>, for the Botswana Harvard AIDS Institute

<sup>1</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA, <sup>2</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>3</sup>Liverpool School of Tropical Medicine, Liverpool, UK

**Background:** Young women in sub-Saharan Africa are at particularly high risk of HIV acquisition. Recent shifts toward 'test and treat' strategies have potential to reduce transmission in this age group, but have not been widely studied outside of clinical trials. Using data from nationwide surveillance among pregnant women in Botswana, where a 'test and treat' strategy began in May 2016, we describe trends in HIV prevalence over time and highlight the opportunity for targeted prevention.

**Methods:** The Tsepamo study abstracted data from obstetric records of all women delivering at eight government hospitals in Botswana between 2015–2019, approximately 45% of all births in the country. Maternal HIV status was documented in >99% of records along with other demographic data. We used descriptive stratified analyses to identify prevalence trends by age group and year. We evaluated decreases in HIV prevalence over time using Cochran–Armitage test for linear trend and performed an adjusted analysis using multivariable logistic regression to identify factors associated with decline in HIV prevalence.

**Results:** Among the 120,755 antenatal records reviewed during the study period, the overall prevalence of HIV infection was 24.1%. Prevalence differed by site of delivery, ranging from 16.1%–28.2% and increased markedly with age (Figure 1). Lower educational attainment (OR=3.28 95% CI 3.07–3.50) and being unmarried (OR=1.98 95% CI 1.88 – 2.08) were associated with HIV infection. Prior pregnancy was a strong risk factor for HIV (OR=2.22 95%CI 2.10–2.29): prevalence was 10.0% with a first pregnancy, 21.0% with a second, and 39.2% with a third or greater. The same age adjusted trends were seen in women aged 15–24, with 2–3-fold increase between a first and third pregnancy (Figure 1). Prevalence decreased linearly during the 5-year study period from 25.8% to 22.7% (p<0.001). Among age specific strata, the greatest absolute decline over the 5-year study period was seen in those ages 25–39, who showed a 5.4% absolute decrease from 2015 to 2019 (Figure 1). Minimal declines were seen in those 15–24, with a decrease of only 1.0% over the same period.

**Conclusion:** While overall trends in Botswana show HIV prevalence declining among pregnant women, prevalence among the youngest age group has remained stagnant. Preventative intervention utilizing pre-exposure prophylaxis (PrEP) should be prioritized during and immediately after the first pregnancy.

589 CLINIC EXPERIENCES ASSOCIATED WITH HIV OUTCOMES AMONG YOUNG MOTHERS LIVING WITH HIV

**Elona Toska**<sup>1</sup>, Lucie Cluver<sup>2</sup>, Siyanai Zhou<sup>1</sup>, Christina Laurenzi<sup>3</sup>, Lorraine Sherr<sup>4</sup>

<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>University of Oxford, Oxford, UK, <sup>3</sup>Stellenbosch University, Cape Town, South Africa, <sup>4</sup>University College London, London, UK

**Background:** Understanding adolescent motherhood and HIV infection in resource-constrained settings is critical. In this study, we report HIV treatment-related outcomes and clinic factors associated with poor treatment outcomes among adolescent mothers living with HIV in South Africa.

**Methods:** All adolescent girls living with HIV from 52 clinics and 9 maternity obstetric units in a health district in South Africa were approached (90.1% and 96% enrolled in each facility type), resulting in n=792 young women living with HIV aged 11–25 participating in the study. Self-reported questionnaires—using validated tools where available—were piloted with n=25 HIV-positive adolescents. Participants who had at least one child before the age of 20 were coded as being adolescent mothers. Analyses included two steps: (1) comparing HIV-related outcomes among adolescent mothers living with HIV (n=354) to nulliparous adolescent girls and young women living with HIV (n=438), and (2) identifying clinic-level factors associated with poor HIV-related outcomes for both groups, using STATA16.1.

**Results:** Socio-demographic characteristics, HIV related outcomes and clinic experiences among participants by motherhood are included in Table 1. Among adolescent mothers living with HIV, n=225 (82.6%) knew their children's HIV-status and fifteen (5%) had at least one child living with HIV. One in six (16%) adolescent mothers living with HIV was not on consistent ART during pregnancy and breastfeeding, and another third (34%) started after the first trimester. Compared to non-mothers, adolescent mothers living with HIV were more likely to report past-week non-adherence (26.0% vs 18.7%, p=0.014), and past-year treatment interruptions (32.8% vs 18.7%, p<0.001). Adolescent mothers were more likely to report ART unavailability due to clinic stock-outs (19.5% vs 13.9%, p=0.036) and be unsatisfied with how they were treated at health facilities during routine care (13.8% vs 7.8%, p=0.005). In multivariate analyses, ART stockouts were associated with past-week non-adherence (aOR32.65 95%CI15.64–68.14, p<0.001) and treatment interruptions (aOR20.72 95%CI 8.85–48.54, p<0.001). Adolescent-sensitive services were associated with lower odds of treatment interruptions (aOR=0.31 95%CI0.09–0.97 p=0.044).

**Conclusion:** More effective and acceptable clinic-based services are critical to treatment adherence and reducing onward HIV-transmission to partners and their HIV-exposed children.

**Table 1 – Socio-demographic characteristics, HIV-related outcomes and clinic experiences by motherhood status**

| Factor (n, % unless noted)   | Adolescent mothers living with HIV (N=354) | Adolescent girls living with HIV (N=438) | Total N=792 | p-value |
|------------------------------|--|--|-------------|---------|
| Age (mean, SD)               | 19.8 (1.9)                                 | 15.9 (2.8)                               | 17.7 (3.1)  | <0.001  |
| Rural residence              | 89 (25.2%)                                 | 106 (24.3%)                              | 195 (24.7%) | 0.757   |
| Informal housing             | 81 (23.9%)                                 | 63 (14.4%)                               | 144 (18.6%) | 0.001   |
| Hunger                       | 106 (29.9%)                                | 91 (20.8%)                               | 197 (24.9%) | 0.003   |
| Clinic experiences           |  |  |             |         |
| ART stock outs (past year)   | 69 (19.5%)                                 | 61 (13.9%)                               | 130 (16.4%) | 0.036   |
| Adolescent-friendly services | 25 (7.1%)                                  | 25 (5.7%)                                | 50 (6.3%)   | 0.436   |
| Support group attendance     | 12 (3.5%)                                  | 37 (8.9%)                                | 49 (6.5%)   | 0.003   |
| Clinic wait time >1 hour     | 230 (65.0%)                                | 229 (52.3%)                              | 459 (58.0%) | <0.001  |
| Confidentiality              | 198 (55.9%)                                | 248 (56.6%)                              | 446 (56.2%) | 0.846   |
| Unsatisfied by services      | 49 (13.8%)                                 | 34 (7.8%)                                | 83 (10.5%)  | 0.005   |

**590 LOWER INSULIN SENSITIVITY EARLY IN LIFE WITH IN UTERO HIV/ART EXPOSURE IN BOTSWANA**

**Jennifer Jao**<sup>1</sup>, Shan Sun<sup>2</sup>, Lauren C. Balmert<sup>1</sup>, Justine Legbedze<sup>2</sup>, Keolebogile N. Mmasa<sup>3</sup>, Gosego N. Masasa<sup>3</sup>, Samuel N. Kgole<sup>3</sup>, Sikhulile N. Moyo<sup>3</sup>, Joseph Makhema<sup>3</sup>, Bornapate Nkomo<sup>4</sup>, Mitchell E. Geffner<sup>5</sup>, Elaine J. Abrams<sup>6</sup>, Mariana Gerschenson<sup>7</sup>, Irwin J. Kurland<sup>8</sup>, Kathleen M. Powis<sup>9</sup>

<sup>1</sup>Northwestern University Feinberg School of Medicine, Chicago, IL, <sup>2</sup>Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, <sup>3</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>4</sup>Botswana Ministry of Health, Gaborone, Botswana, <sup>5</sup>Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, <sup>6</sup>ICAP at Columbia University, New York, NY, USA, <sup>7</sup>University of Hawaii, Honolulu, HI, USA, <sup>8</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>9</sup>Massachusetts General Hospital, Boston, MA, USA

**Background:** Few data exist on early life metabolic perturbations in newborns with in utero HIV and antiretroviral therapy (ART) exposure who are HIV uninfected (HEU).

**Methods:** We measured pre-prandial insulin and glucose at birth (within 72 hours of life) and 1 month (mo) to calculate Homeostasis Model Assessment for Insulin Resistance (HOMA) in newborns HEU and newborns HIV-unexposed uninfected (HUU) enrolled in the Tshilo Dikotla study in Botswana from 2016-2019. Data on socio-demographics, family history of diabetes (DM), maternal body mass index (BMI), gestational DM (GDM), HIV disease, and ART history, as well as newborn gestational age (GA), anthropometrics, and feeding were collected. HOMA was log-transformed; Z scores for birth weight (BWZ) and length (BLZ) were calculated. Linear mixed models were fit to assess the association between in utero HIV/ART exposure and average HOMA from birth to 1 mo of age, adjusting for confounders. Subgroup analyses were performed in newborns HEU to assess the association of in utero ART [tenofovir (TDF)/emtricitabine (FTC)/dolutegravir (DTG) vs. TDF/FTC/efavirenz (EFV)] with HOMA.

**Results:** Of 450 newborns, 144 were HUU. Maternal age (30 vs. 24 years, p<0.001) and proportion completing ≤ secondary school education (89% vs. 69%, p<0.001) was higher among women of newborns HEU vs. HUU respectively; family history of DM, maternal BMI, GDM, and tobacco/alcohol/substance use, as well as newborn GA, BWZ, BLZ, and proportions of newborns exclusively breastfed in the first mo of life were similar between groups. Among mothers of newborns HEU, 47% had a CD4 >500 cells/mm<sup>3</sup> and 93% a viral load (VL) <40 copies/mL at enrollment, 56% were on ART at conception, 59% received TDF/FTC/DTG and 41% TDF/FTC/EFV. Median birth and 1 mo HOMA was 0.38 vs. 0.30 and 0.76 vs. 0.62 for newborns HEU vs. HUU respectively. Mean log HOMA from birth to 1 mo of age was 0.68 units (p=0.037) higher in newborns HEU vs. HUU after adjusting for family history of DM, maternal age, education, BMI, and GDM, as well as newborn sex, preterm birth, and birth anthropometrics. (Table) Among newborns HEU, there was no association between in utero ART and HOMA from birth to 1 mo of age after adjusting for maternal CD4, VL and ART use at conception in addition to the confounders above.

**Conclusion:** In this cohort, newborns HEU had lower insulin sensitivity compared to those HUU from birth to 1 mo. Future studies to evaluate the long-term significance of this early life metabolic alteration are warranted.

**Table. Linear Mixed Models Showing Unadjusted and Adjusted Mean Differences in Log HOMA from Birth to 1 Month of Life by Predictor of Interest**

| Model  | Unadjusted Coefficient | p value | Adjusted Coefficient | p value |
|--|------------------------|---------|----------------------|---------|
| <i>Model 1 (including all infants HEU and HUU) *</i> |                        |         |                      |         |
| HEU vs. HUU  | 0.064                  | 0.027   | 0.068                | 0.037   |
| <i>Model 2 (only infants HEU) ^</i>                  |                        |         |                      |         |
| In utero TDF/FTC/DTG vs. TDF/FTC/EFV                 | -0.048                 | 0.118   | -0.021               | 0.580   |

DTG=dolutegravir; EFV=efavirenz; FTC=emtricitabine; HEU=HIV-exposed uninfected; HOMA-IR=Homeostatic Model Assessment-Insulin Resistance; HUU=HIV-unexposed uninfected; TDF=tenofovir

\* Adjusted for family history of diabetes, maternal age, education, body mass index, and gestational diabetes, as well as newborn sex, preterm birth, and birth weight Z score.

^ Adjusted for family history of diabetes, maternal age, education, body mass index, gestational diabetes, CD4 count, HIV RNA level, and ART use at conception, as well as newborn sex, preterm birth, and birth weight Z score.

**591 IMMUNOLOGIC PREDICTORS OF NEURODEVELOPMENT IN HIV-EXPOSED AND -UNEXPOSED CHILDREN**

**Alka Khaitan**<sup>1</sup>, Jeong H. Jang<sup>1</sup>, We Li<sup>1</sup>, Eren Oyungu<sup>2</sup>, Qigui Yu<sup>1</sup>, Megan McHenry<sup>1</sup>

<sup>1</sup>Indiana University, Indianapolis, IN, USA, <sup>2</sup>Moi University, Eldoret, Kenya

**Background:** Children who are HIV-exposed, uninfected (HEU) have worse neurodevelopmental (ND) outcomes compared to children who are HIV-unexposed (HU), but assessing ND in resource-poor settings is challenging. We measured cognitive, language and motor development in HEU and HU paired with pro- and anti-inflammatory plasma biomarkers in each child to identify potential biomarkers of poor ND outcomes.

**Methods:** We enrolled 82 Kenyan children (44 HEU and 38 HU) between ages 18-36 months old. 81 plasma biomarkers, including cytokines, chemokines, growth factors and soluble immune checkpoints, were quantified using magnetic bead based multiplex assays. ND was measured using the Bayley Scales of Infant and Toddler Development, 3rd edition. Composite scores for cognition, language, and motor domains were used for the analysis. We computed Spearman's rank correlations of 81 plasma biomarkers and 6 demographic/social/clinical factors (age, gender, WAMI [water/sanitation/income], maternal education, prematurity and malnutrition) with cognitive, language and motor scores. To identify predictors of ND, variables with p<0.1 from the Spearman's correlation test were jointly considered in a multiple linear regression model, and Bayesian model averaging (BMA) was performed to identify a parsimonious subset of those most useful for predicting ND outcomes, with a posterior inclusion probability (PIP) ≥0.5 considered as significant.

**Results:** The correlation analysis resulted in 2, 6 and 10 variables with p<0.1 for cognitive, language and motor scores respectively to input the BMA for HEU. Fibroblast growth factor-2 (FGF2) predicted language scores (PIP=0.64) and IL-22 predicted motor development (PIP=0.75) in HEU. In HU, the correlation analysis resulted in 16, 15, and 5 variables for cognitive, language and motor scores respectively to input the BMA. Hepatocyte growth factor (HGF) and IL-5 predicted cognitive scores (PIP=0.68 and 0.62) and CXCL13 and IL-7 predicted motor outcomes (PIP=0.59 and 0.51). Language scores in HU were predicted by maternal education (PIP=0.79), IL-1a (PIP=0.67), IL-2R (PIP=0.84), and IL-5 (PIP=0.76).

**Conclusion:** Immunologic biomarkers predicted ND outcomes more frequently than social, demographic and clinical factors. The predictors of cognitive, motor and language outcomes differed between HU and HEU. Interestingly, IL-22, an inflammatory cytokine was the strongest predictor in HEU while CD25, an anti-inflammatory cytokine receptor (IL-2R), was the strongest in HU.

**592 GROWTH FALTERING AND DEVELOPMENTAL DELAYS IN HIV-EXPOSED UNINFECTED INFANTS IN UGANDA**

**Reshma Sirajee**<sup>1</sup>, Andrea L. Conroy<sup>2</sup>, Sophie Namasopo<sup>3</sup>, Robert O. Opoka<sup>4</sup>, Stephanie Lavoie<sup>5</sup>, Sarah Forgie<sup>1</sup>, Bukola O. Salami<sup>1</sup>, Michael T. Hawkes<sup>1</sup>

<sup>1</sup>University of Alberta, Edmonton, Canada, <sup>2</sup>Indiana University, Indianapolis, IN, USA, <sup>3</sup>Jinja Regional Referral Hospital, Jinja, Uganda, <sup>4</sup>Makerere University, Kampala, Uganda, <sup>5</sup>National Microbiology Laboratory, Winnipeg, Canada

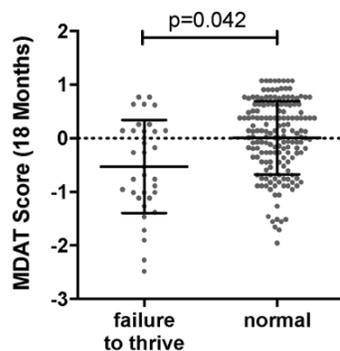
**Background:** HIV exposed but uninfected infants (HEU) are at increased risk of impaired early linear growth and cognitive development. We examined associations between pre and postnatal growth and subsequent neurodevelopment in Ugandan HEUs, hypothesizing that early insults may explain alterations in both somatic growth and brain development.

**Methods:** We prospectively followed a cohort of HEUs from birth to 18 months of age. The height, weight, head circumference, and mid-upper arm circumference (MUAC) were collected and compared to the World Health

Organization growth charts. The Malawi Development Assessment Test (MDAT) was performed at 12 and 18 months of age to examine developmental milestones. The Color Object Association Test (COAT) was used at 18 months of age to assess declarative memory.

**Results:** 375 mother-child pairs were enrolled. Mothers were median 28 years old and 32% had a known diagnosis of HIV prior to pregnancy. The cohort included HEUs who were female (53%), premature (11%) and had low birth weight (LBW) (7.6%). Follow up was completed at 6 weeks (n=147 HEUs), 12 months (n=109 HEUs), and 18 months (n=170 HEUs) of age. Eight infants tested positive for HIV and were excluded from the study. 197 HEUs were lost to follow-up at 18 months of age. The final cohort consisted of 170 HEUs who completed the MDAT at 18 months of age. The number of HEUs stunted (32%), 43%, and 58%) and underweight (7.4%, 15% and 15%) increased at 6 weeks, 12 months and 18 months of age respectively. HEUs had behavioral scores on the MDAT that were similar to the reference children population. The mean score on the COAT was 5.5 compared to 6.9 in the reference children population. The MDAT score at 18 months of age showed cross-sectional correlation with weight- ( $p=0.36$ ,  $p<0.0001$ ), height- ( $p=0.41$ ,  $p<0.0001$ ), head circumference- ( $p=0.26$ ,  $p=0.0011$ ), and MUAC-for-age ( $p=0.34$ ,  $p=0.0014$ ). Failure to thrive (FTT), defined as crossing two major percentile lines downward on the weight-for-age growth chart, was observed in 21% HEUs during the first 18 months of life. Failure to thrive (FTT) was associated with lower MDAT scores ( $p=0.042$ ) at 18 months of age. Lower weight-for-height z-scores were associated with lower COAT scores ( $p=0.32$ ,  $p=0.0017$ ). LBW (<2500g) predicted lower MDAT score ( $p=0.0010$ ) at 18 months of age.

**Conclusion:** In a prospective cohort of HEUs in Uganda, LBW, stunting, and FTT were common and were associated with lower attainment of developmental milestones and lower declarative memory at 18 months.



**Figure 1. Association between failure to thrive (FTT) and neurodevelopment among HEUs.** Infants with FTT from 6 weeks to 18 months of age had median MDAT standardized ability score of -0.13 (IQR -0.75 to +0.14) compared to infants without FTT, median +0.14 (IQR -0.44 to +0.63),  $p=0.042$ .

children and adolescents. Potential influences included executive function, cognitive efficiency (working memory [WMI] and processing speed [PSI]), behavioral/social-emotional functioning, caregiver mental/physical health, HIV disease markers for YAPHIV, and total adversity (adverse life events plus cognitive/behavioral/social-emotional risks and caregiver health). The most recent AMP assessment was used for each influence; outcomes were measured at Year 1 in AMP Up. Separate robust Poisson regression models were fit to evaluate associations between each influence and each outcome, adjusting for demographic factors and PHIV status (also considered as an effect modifier). Multiple imputation was used for missing data.

**Results:** Participants (N=315; YAPHIV=228) were 58% female, 67% Black, 27% Hispanic. Compared to YAPHEU, YAPHIV were older (mean 20.8 vs 20.2 years) and more often from families with higher median income. In adjusted models (Figure), high school graduation and postsecondary education were more likely in those with higher cognitive efficiency, higher parent-reported executive function, and lower total adversity. For high school graduation, age-appropriate behavior (per parent report) was an additional asset. For postsecondary education, additional assets were age-appropriate adaptive skills (parent and child reports) and lack of difficulty in emotional functioning (child report). Current employment was associated with higher cognitive efficiency and, among YAPHIV, lower nadir CD4. PHIV status did not modify associations.

**Conclusion:** Different skill sets affect attainment of academic vs employment milestones. To promote resilience, targeted services addressing cognitive or behavioral challenges in childhood and adolescence may encourage attainment of milestones among young adults affected by HIV.

**Adjusted associations of influences and attainment of young adult milestones**

|  | High School       | Postsecondary      | Currently Working |
|--|-------------------|--------------------|-------------------|
| BRIEF parent report, behavioral regulation index: T-score < 65 <sup>1</sup>      | 1.39 (1.06, 1.82) | 1.61 (0.92, 2.85)  | 1.21 (0.85, 2.02) |
| BRIEF parent report, meta-cognition index: T-score < 65 <sup>1</sup>             | 1.23 (1.03, 1.47) | 1.38 (0.96, 1.98)  | 1.10 (0.82, 1.49) |
| Wechsler working memory index (WMI; ref: < 70)                                   |                   |                    |                   |
| WMI: ≥ 85  | 1.22 (0.96, 1.55) | 7.84 (2.06, 29.87) | 2.31 (1.18, 4.53) |
| WMI: 70 - 84   | 1.09 (0.84, 1.40) | 5.63 (1.47, 21.58) | 2.01 (1.00, 4.02) |
| Wechsler processing speed index (PSI; ref: < 70)                                 |                   |                    |                   |
| PSI: ≥ 85  | 1.13 (0.85, 1.50) | 2.22 (1.00, 4.91)  | 1.81 (0.90, 3.65) |
| PSI: 70 - 84   | 0.98 (0.72, 1.34) | 1.36 (0.58, 3.18)  | 1.24 (0.58, 2.62) |
| BASC-2 parent report, externalizing problem index: T-score < 60 <sup>1</sup>     | 1.18 (0.97, 1.43) | 0.94 (0.67, 1.32)  | 1.07 (0.78, 1.46) |
| BASC-2 parent report, behavioral symptoms index: T-score < 60 <sup>1</sup>       | 1.25 (1.02, 1.53) | 0.99 (0.70, 1.38)  | 1.14 (0.82, 1.58) |
| BASC-2 parent report, adaptive skills index: T-score > 40 <sup>1</sup>           | 1.11 (0.97, 1.28) | 1.32 (0.96, 1.80)  | 1.14 (0.87, 1.48) |
| BASC-2 child self-report, internalizing problem index: T-score < 60 <sup>1</sup> | 1.05 (0.87, 1.25) | 1.51 (0.94, 2.42)  | 0.98 (0.70, 1.36) |
| BASC-2 child self-report, emotional symptoms index: T-score < 60 <sup>1</sup>    | 1.00 (0.83, 1.20) | 1.61 (0.94, 2.75)  | 0.92 (0.65, 1.30) |
| BASC-2 child self-report, personal adjustment index: T-score > 40 <sup>1</sup>   | 1.10 (0.91, 1.33) | 1.73 (1.02, 2.94)  | 1.20 (0.82, 1.76) |
| Adversity index, total number of risks: per one-unit increase                    | 0.96 (0.94, 0.99) | 0.94 (0.88, 1.00)  | 0.98 (0.93, 1.03) |
| Nadir CD4 (YAPHIV only; ref: < 200 cells/mm <sup>3</sup> )                       |                   |                    |                   |
| ≥ 500  | 0.94 (0.80, 1.10) | 0.86 (0.57, 1.30)  | 0.66 (0.44, 0.98) |
| 200 - 499  | 0.90 (0.79, 1.03) | 0.98 (0.73, 1.33)  | 0.75 (0.56, 1.00) |

aPR: Adjusted prevalence ratio for attainment of a specific milestone comparing participants with a specific influence vs reference group.

Each model adjusted for PHIV infection status, sex, race/ethnicity, Wechsler Full Scale IQ (FSIQ), family SES index (included annual income and household density), and age at time of measurement of each influence. FSIQ was excluded from models for the WMI and PSI.

High school graduation: attainment of high school diploma, GED, or enrollment in higher education. Postsecondary education: enrollment in technical/trade schools, college, associate and bachelor degrees, or graduate/professional school. Currently working: full- or part-time employment.

BRIEF: Behavior Rating Inventory of Executive Function; Wechsler: Wechsler Intelligence Scale for Children, 4th Ed. or Wechsler Adult Intelligence Scale, 4th Ed.; BASC-2: Behavior Assessment System for Children, 2nd Ed.; Adversity Index: study-specific summary measure of risks.

<sup>1</sup> Indicates lower frequency or intensity of problems.

## 593 MARKERS OF RESILIENCE IN YOUNG ADULTS WITH PERINATAL HIV EXPOSURE OR INFECTION

Patricia A. Sirois<sup>1</sup>, Yanling Huo<sup>2</sup>, Molly Nozyce<sup>3</sup>, Patricia A. Garvie<sup>4</sup>, Lynnette L. Harris<sup>5</sup>, Kathleen Malee<sup>6</sup>, Robin McEvoy<sup>7</sup>, Claude A. Mellins<sup>8</sup>, Sharon L. Nichols<sup>9</sup>, Renee Smith<sup>10</sup>, Katherine Tassiopoulos<sup>2</sup>, for the Pediatric HIV/AIDS Cohort Study (PHACS)

<sup>1</sup>Tulane University, New Orleans, Louisiana, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Jacobi Medical Center, Bronx, NY, USA, <sup>4</sup>Children's Diagnostic & Treatment Center, Fort Lauderdale, FL, USA, <sup>5</sup>Baylor College of Medicine, Houston, TX, USA, <sup>6</sup>Northwestern University, Chicago, IL, USA, <sup>7</sup>University of Colorado, Aurora, CO, USA, <sup>8</sup>Columbia University, New York, NY, USA, <sup>9</sup>University of California San Diego, La Jolla, CA, USA, <sup>10</sup>University of Illinois at Chicago, Chicago, IL, USA

**Background:** Resilience is defined as positive adaptation in the context of risk or adversity. Perinatal HIV exposure (PHEU) or infection (PHIV) can adversely affect youth development, yet few studies have examined resilience in young adults with PHEU (YAPHEU) or PHIV (YAPHIV). We evaluated factors contributing to resilience, marked by attainment of three milestones in the transition from adolescence to adulthood: high school graduation, postsecondary education, and current employment.

**Methods:** In this prospective analysis, prevalence of each milestone was calculated for YAPHIV and YAPHEU age 19+ enrolled in the young adult PHACS AMP Up cohort who were previously followed in the PHACS AMP study of

## 594 DISCOVERY OF LARGE CLONES IN CHILDREN CARRYING PROVIRUSES CONSISTING OF A SINGLE LTR

Johannes C. Botha<sup>1</sup>, Mary-Grace Katusiime<sup>2</sup>, Michael J. Bale<sup>3</sup>, Mark F. Cotton<sup>1</sup>, Mary F. Kearney<sup>2</sup>, John W. Mellors<sup>4</sup>, Gert Van Zyl<sup>1</sup>

<sup>1</sup>Stellenbosch University, Cape Town, South Africa, <sup>2</sup>National Cancer Institute, Frederick, MD, USA, <sup>3</sup>Cornell University, Ithaca, NY, USA, <sup>4</sup>University of Pittsburgh, Pittsburgh, PA, USA

**Background:** A prior study revealed that HIV-infected T cell clones arise rapidly in children born with HIV and that clones can persist for at least 9 years on ART. Little is known, however, about the proviral structures within the clones and about their dynamics over time. We investigated the proviral structures and the dynamics of the most expanded T cell clones in early treated children using new approaches to quantify and genetically characterize proviruses within cell clones.

**Methods:** Clones were investigated in children with suppressed viremia on ART for >8 years after initiating treatment at a median age of 6.1 months (range: 1.8-9.9). A new integration site specific proviral amplification (ISSPA) assay was designed to characterize the proviruses in large cell clones identified by standard integration site analysis. Primers were used to amplify the full-length HIV from either the 5' or 3' proviral-host junction to the human genome and/or from each LTR-host junction. Clones were also quantified

at 3 timepoints spanning 1.5 years with an integration site specific proviral absolute quantification (ISSAQ) assay using a digitalized nested real-time PCR approach. ISSAQ is normalized for cellular input and targets the human genome region adjacent to the integration site in the first round of PCR and the unique integration site junction in the second round.

**Results:** 9 large clones comprising 1-12.5% of all integration sites detected were evaluated in 5 children (Table 1). The provirus in 8 of the 9 clones consisted only of a single, full-length LTR. The 9th clone had a LTR with a 240bp deletion spanning the R region. ISSAQ showed a statistically significant change in clone size in 2 of the 9 clones in two different children: one increased in size from 22 to 140 integration events per 1 million cells and the other decreased from 15 to 2. The other 7 infected cell clones remained remarkably stable in size over the 1.5-year sampling interval.

**Conclusion:** The largest cell clones in children contained highly defective proviruses consisting of a single LTR or partial LTR. Most of these clones were stable in size but a subset showed large changes. Whether early treatment in children enriches for clones with highly defective proviruses or if such clones are more common than previously recognized is unknown. The effects of single LTRs on cellular function should be investigated as they contain promotor sequences.

| Patient | Age at ART initiation (months) | Time to viral suppression (years) | Integrant chromosome/orientation | Gene/orientation | % of total integrations detected | Provirus    |
|---------|--------------------------------|-----------------------------------|----------------------------------|------------------|----------------------------------|-------------|
| 1       | 9.9                            | 0.92                              | C1/+                             | SRSF10/-         | 5.8%                             | Single-LTR  |
|         |                                |                                   | C1/-                             | TTC13/-          | 1.3%                             | Single-LTR  |
|         |                                |                                   | C11/-                            | RAB6A/-          | 1.9%                             | Single-LTR  |
| 2       | 9.3                            | 2.29                              | C2/-                             | ALMS1/+          | 1%                               | Single-LTR  |
|         |                                |                                   | C6/-                             | RANBP9/-         | 1.3%                             | Single-LTR  |
| 3       | 2.7                            | 1.38                              | C14/-                            | RADS1B/+         | 4.4%                             | Single-LTR  |
|         |                                |                                   | C6/-                             | Intergenic       | 2.2%                             | Single-LTR  |
| 4       | 6.1                            | 0.47                              | C6/-                             | Intergenic       | 6.4%                             | Partial-LTR |
| 5       | 1.8                            | 0.46                              | C6/-                             | Intergenic       | 12.5%                            | Single-LTR  |

Proviral and gene orientation is indicated with + referring to forward and - to reverse

**595 TOTAL HIV DNA LEVELS CORRELATE WITH PLASMA IL-2 LEVELS IN THAI INFANTS BUT NOT ADULTS**

**Julie Mitchell**<sup>1</sup>, Thanyawee Puthanakit<sup>2</sup>, Kenneth Dietze<sup>1</sup>, Marta Massanello<sup>3</sup>, Pope Kosalaraksa<sup>4</sup>, Suparat Kanjanavanit<sup>5</sup>, Thitiporn Borkird<sup>6</sup>, Piyarat Suntarattiwong<sup>7</sup>, Panadda Sawangsinth<sup>8</sup>, Mark de Souza<sup>8</sup>, Jintanat Ananworanich<sup>1</sup>, Merlin Robb<sup>1</sup>, Nicolas Chomont<sup>3</sup>, Lydie Trautmann<sup>1</sup>, for the HIVNAT209 Study Group

<sup>1</sup>US Military HIV Research Program, Silver Spring, MD, USA, <sup>2</sup>HIV-NAT, The Thai Red Cross AIDS Research Center, Bangkok, Thailand, <sup>3</sup>Centre de Recherche du CHUM, Montreal, Canada, <sup>4</sup>Khon Kaen Hospital, Khon Kaen, Thailand, <sup>5</sup>Nakornping Hospital, Chiang Mai, Thailand, <sup>6</sup>Hat Yai Hospital, Songkhla, Thailand, <sup>7</sup>Queen Sirikit National Institute of Child Health, Bangkok, Thailand, <sup>8</sup>SEARCH, Bangkok, Thailand

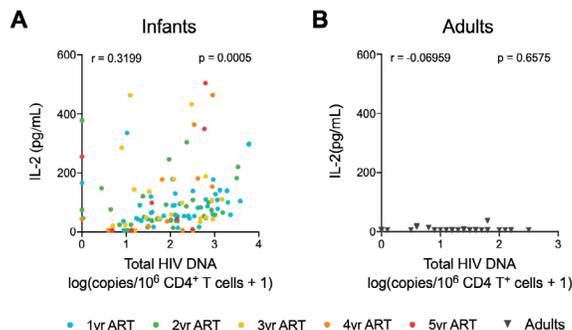
**Background:** The infant immune response to infection differs from that of adults, with decreased Th1 cytokine production and more rapid HIV disease progression. We measured the production of cytokines in plasma samples from vertically HIV-infected Thai infants at the time of diagnosis and annually after suppressive early antiretroviral therapy (ART).

**Methods:** Plasma samples from 92 vertically infected Thai infants living with HIV who were enrolled in the HIVNAT209 study were analyzed. Infants initiated ART immediately after diagnosis within the first 6 months of life (median 2 mo.). Samples were collected within 1 week of ART initiation (n=34) and yearly thereafter through 5 years of suppressive ART (n=134 total). Plasma cytokine levels were measured by Luminex. Total HIV DNA levels were measured in blood CD4+ T cells by real-time PCR. Comparisons were made with 42 Thai adults living with HIV who initiated ART in acute HIV infection (AHI), HIV exposed uninfected infants (HEU, n=10, median 15 mo. old), and HIV- adults (n=9).

**Results:** At the time of ART initiation, infants had higher levels of CXCL13, IL-2, and TNFα (p<0.0001), IL-8 and TSLP (p<0.001), and MIP-1α (p<0.05) than adults with AHI despite the latter having higher viral loads (p<0.001). Levels of CXCL13, IP-10, and MIP-1α correlated with plasma viral load at the time of ART initiation in both adults and infants, whereas IFNα, IL-2, TSLP, IL-8, sCD40L, and TNFα correlated with viral load in infants only. Following ART, children maintained higher levels of CXCL13, IL-2, MIP-1α, sCD40L, TNFα, and TSLP (p<0.0001), IL-8 (p<0.001), and IFNα (p<0.01) than adults. To determine if the elevated cytokine levels are driven by age or HIV status, we compared plasma cytokine

levels in HEU and HIV- adults. We found higher levels of sCD40L (p<0.001), CXCL13 and IL-2 (p<0.01), and TSLP (p=0.05) in HEU compared to HIV- adults, suggesting that these cytokines are elevated in infants regardless of HIV status. Interestingly the levels of plasma IL-2 correlated with total HIV DNA levels in children on successful ART (r=0.32, p<0.001), but not in adults (Fig 1).

**Conclusion:** Infants produced robust cytokines both at diagnosis and after ART, many at higher levels than adults living with HIV. In infants on ART, plasma IL-2 levels correlated with total HIV DNA levels. As IL-2 levels were also elevated in HEU, these data suggest that higher IL-2 levels may drive seeding, proliferation, or survival of latently infected cells, and thus reservoir persistence, in children.



**596 FASTER INITIAL VIRAL DECAY IN FEMALE CHILDREN LIVING WITH HIV**

**Sara Domínguez-Rodríguez**<sup>1</sup>, Miquel Serna-Pascual<sup>1</sup>, Caroline Foster<sup>2</sup>, Paolo Palma<sup>3</sup>, Eleni Nastouli<sup>4</sup>, Anita De Rossi<sup>5</sup>, Javier Seoane<sup>6</sup>, Paolo Rossi<sup>7</sup>, Carlo Giaquinto<sup>8</sup>, Alfredo Tagarro<sup>9</sup>, Pablo Rojo<sup>9</sup>, for the EPIICAL Consortium

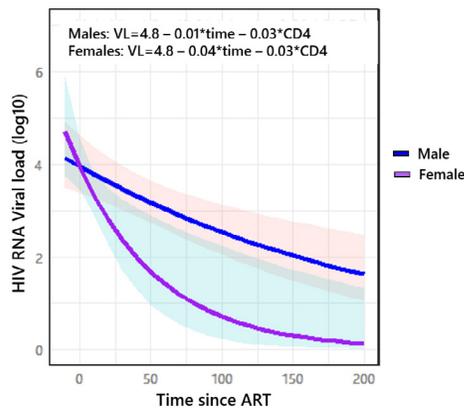
<sup>1</sup>Fundación para la Investigación Biomédica del Hospital 12 de Octubre, Madrid, Spain, <sup>2</sup>Imperial College Healthcare NHS Trust, London, United Kingdom, <sup>3</sup>Division of Immune and Infectious Diseases, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, <sup>4</sup>Department of Population, Policy and Practice, UCL Great Ormond Street Institute of Child Health, London, UK, <sup>5</sup>Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy, <sup>6</sup>Terrestrial Ecology Group, Department of Ecology, Universidad Autónoma de Madrid, Madrid, Spain, <sup>7</sup>Division of Immune and Infectious Diseases, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, <sup>8</sup>Department of Surgery, Oncology and Gastroenterology, Section of Oncology and Immunology, University of Padova, Padova, Italy, <sup>9</sup>Pediatric Infectious Diseases Unit, Fundación para la Investigación Biomédica del Hospital 12 de Octubre, Madrid, Spain

**Background:** Women living with HIV have lower HIV RNA levels and higher CD4 cell counts than men. However, limited data exist regarding sex bias and viral decay in children with HIV. We investigated the sex differences in viral decay and control of viremia in HIV perinatally infected children who suppressed viral load within 12-months of treatment initiation and describe the association between viral decay and DNA reservoir size.

**Methods:** We analysed data from 25 patients from four European cohorts of perinatally infected children (CARMA Study). We estimated the breakpoints on viral decay trends to distinguish viremia control phases and slopes using a piecewise regression model. The effect of sex on the viral decay was analysed using a multivariable mixed model regression and cell lifespan was extrapolated using the ushr tool. The association between viral decay in phase-I and DNA reservoir size was estimated using a multivariable Poisson regression model.

**Results:** Females (n=17, 68%) and males presented similar HIV RNA levels (5.7 [5.25;6.0] vs. 5.7 [5.13;5.81, p=0.883]) and % CD4 (29.0 cells/mm<sup>3</sup> [18.0;36.25] vs. 31.5 [20.75;41.75]) at ART initiation. No differences were found between sexes relating age at ART, age at HIV diagnosis, or time to suppression. However, females reached phase-II significantly earlier than male (3.0 months [1.44;4.85] vs. 6.79 months [5.14;9.94], p=0.023). For each month elapsed, females had faster viral decay than male (interaction coefficient= -0.01±0.001).

**Conclusion:** Females presented faster phase-I viral decay regardless their age at ART initiation, baseline %CD4, or baseline RNA levels.



## 597 INCREASED IMMUNE ACTIVATION AND EXHAUSTION IN VERTICALLY HIV-1-INFECTED YOUNG ADULTS

Laura Tarancon-Diez<sup>1</sup>, Itziar Carrasco<sup>1</sup>, Elena Vázquez Alejo<sup>1</sup>, Santiago Jiménez de Ory<sup>1</sup>, Talía Sainz<sup>2</sup>, Miren A. Apilanez<sup>3</sup>, Pablo Rojo<sup>4</sup>, Sara Guillén<sup>5</sup>, José Tomás Ramos<sup>6</sup>, María Ángeles Muñoz-Fernández<sup>1</sup>, María Luisa Navarro<sup>1</sup>

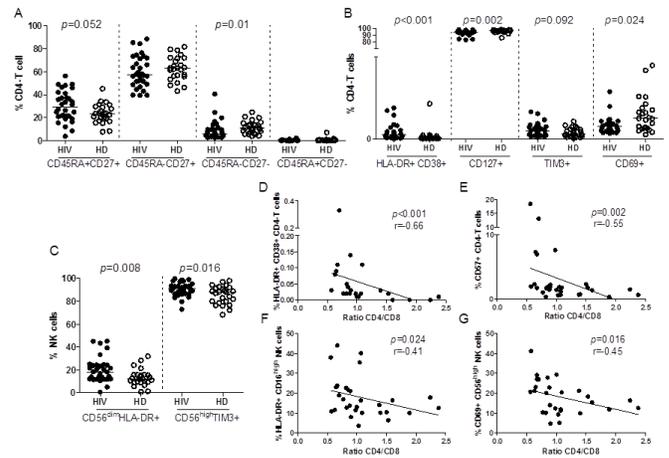
<sup>1</sup>University Hospital Gregorio Marañón, Madrid, Spain, <sup>2</sup>Hospital La Paz Institute for Health Research, Madrid, Spain, <sup>3</sup>Hospital Donostia, San Sebastián, Spain, <sup>4</sup>Hospital Universitario 12 de Octubre, Madrid, Spain, <sup>5</sup>Hospital Universitario de Getafe, Madrid, Spain, <sup>6</sup>Hospital Universitario Clínico San Carlos, Madrid, Spain

**Background:** Vertically HIV-infected children show irreversible immune damage associated with HIV-1 infection and early antiretroviral treatment (ART) exposure. The objective of the study is to assess immune activation and senescence of vertically HIV-infected patients once they reach adulthood compared to non-HIV-infected subjects

**Methods:** Vertically HIV-infected group (HIV n=32) under suppressive ART for at least 5 years were selected from the Paediatric AIDS Research Network of Spain (coRISpe) and cryopreserved samples from the Spanish HIV BioBank. HIV group was compared with a non-HIV-infected Healthy Donors group (HD n=28) matched by age and sex. Subset distribution and activation, proliferation, senescence and exhaustion markers on T cells and natural killer (NK) cells was studied on peripheral blood mononuclear cells by multiparametric flow cytometry

**Results:** HIV (24 years [IQR:22-28] median age, 12% male, 794 [IQR:599-981] median CD4-T cells, 198 [IQR:76-330] median CD4+ Nadir, 4 [IQR:1-6] years median age at ART initiation, 20 [IQR:18-23] years since ART initiation and 8 [IQR:7-10] years under virological control) show differences in CD4-T maturation subsets (defined by CD45RA and CD27 expression, Fig A), high HLA-DR/CD38, CD127, TIM-3 and low CD69 expression on CD4-T (Fig B) and CD8-T cell subsets compared with HD. Regarding NK phenotype, HIV showed low frequency of CD56dim (p=0.057), CD16high (p=0.02), high percentage of CD56high NK subsets (p=0.166); and increased levels of HLA-DR and TIM-3 expression on CD56dim and CD56high subsets compared with HD (Fig C). Focusing on HIV, strong and direct correlations were observed between activation and senescence (HLA-DR CD38 and CD57, Fig D-E) and exhaustion (TIGIT, PD-1, p=0.002; r=-0.76, p=0.013; r=-0.45 respectively) on CD4-T cells with CD4/CD8 Ratio. On NK cells, HLA-DR and CD69 (Fig F-G) NKG2D and NKG2A expression correlated with CD4/CD8 Ratio (p=0.027; r=0.40, p=0.033; r=0.39 respectively). Direct associations between age at ART initiation and frequency of CD16high NK subset and expression of exhaustion (CD57, TIM3) and activation (Nkp30) markers on NK subsets were also observed (p=0.08; r=0.31, p=0.02; r=0.41, p=0.06; r=0.32 respectively)

**Conclusion:** Vertical HIV infection leads to an irreversible immune damage not normalized once adulthood is reached, shown by an increased activation and exhaustion levels in adaptive and innate immune components that are associated with clinical parameters including ratio CD4/CD8 and age at ART initiation



## 598 VIRAL-RESERVOIR LANDSCAPE IN EARLY-TREATED VERTICALLY HIV-1-INFECTED ADOLESCENTS

Libera Sessa<sup>1</sup>, Xiaodong Lian<sup>1</sup>, Ce Gao<sup>1</sup>, Nicola Cotugno<sup>2</sup>, Alessandra Ruggiero<sup>2</sup>, Xu G. Yu<sup>1</sup>, Paolo Palma<sup>2</sup>, Mathias Lichterfeld<sup>1</sup>

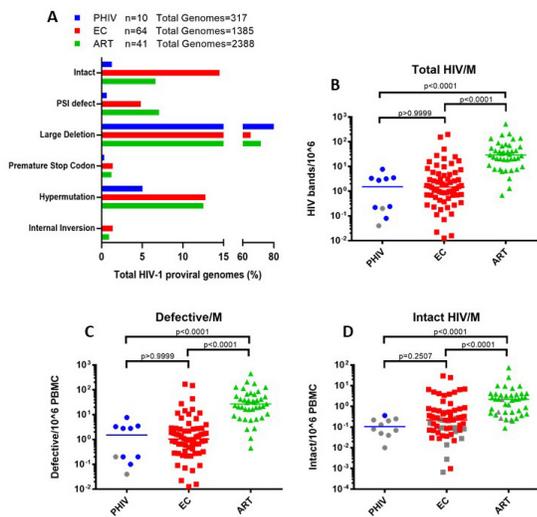
<sup>1</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, <sup>2</sup>Bambino Gesù Children's Hospital, Rome, Italy

**Background:** Perinatally HIV-1 infected adolescents and young adults (PHIV), who started ART therapy very early in their life with no history of viral failure, represent a unique cohort to characterize the effects of long-term ART on viral reservoir structure and composition.

**Methods:** 10 PHIV who initiated ART at a mean age of 4 months with durable viral control (plasma HIV-RNA <50cp/mL) since treatment initiation (median 15 years) were enrolled at Bambino Gesù Children's Hospital. For comparison, 41 HIV-1 ART-treated adults (ART) with undetectable viral loads for a median of 9 years (range, 2-19) and 64 untreated HIV-1 Elite Controller (ECs) with undetectable viral loads for a median of 9 years (range, 1-24 years) were included in this study. Genomic DNA was extracted from total PBMCs and diluted to single genome levels, followed by near full-length next generation viral sequencing. Overall, a median of 9.3x10<sup>6</sup>, 6.6x10<sup>6</sup> and 1.9x10<sup>6</sup> PBMCs were analyzed in PHIV, ECs and ART, respectively.

**Results:** We obtained 317, 1385 and 2388 individual proviral sequences in PHIV, ECs and ART, respectively. The proportion of both intact and defective proviral sequences with hypermutations, internal inversions, premature stop codons and PSI defects was significantly higher in ART and ECs compared to PHIV, while there was no difference in terms of large deletion between the 3 groups (A). Importantly, we found that the median frequency of total (B) and defective (C) HIV-1 DNA sequences in PHIV was significantly lower than in ART-treated adults (p<0.0001), whereas there was no difference between PHIV and EC. Intact proviral sequences were detected in 1 out of 10 PHIV, and their relative frequency was similar between EC and PHIV (0.2 copies/million in ECs vs 0.1 copies/million in PHIV); in contrast, the frequency of intact HIV-1 sequences was significantly lower in PHIV compared to ART-treated adults (0.1 copies/million in PHIV vs 2.1 copies/million in ART, p<0.0001). Notably, all intact sequences detected in PHIV were part of a sequence-identical clone. Interestingly, 1 PHIV, who started ART at 5 months, under treatment for a recorded time of 24 years, showed 19 defective and no intact proviral sequences in more than 80 million PBMCs.

**Conclusion:** These data suggest that PHIV display a viral reservoir landscape similar to ECs but significantly different from ART-treated adults. Future studies will be necessary to characterize the specific characteristics of early-treated and long-term virally suppressed adolescents.



**599 AUTOLOGOUS INFANT ADCC RESPONSES CORRELATE WITH LOWER MTCT AND BETTER OUTCOMES**

**Allison S. Thomas**<sup>1</sup>, Yvetane Moreau<sup>2</sup>, Manish Sagar<sup>2</sup>  
<sup>1</sup>Boston University, Boston, MA, USA, <sup>2</sup>Boston Medical Center, Boston, MA, USA  
**Background:** Previous studies have shown that neutralizing antibody (nAb) responses do not account for the lack of HIV-1 transmission from infected mothers to their breastfed infants. We hypothesize that antibodies capable of inducing antibody-dependent cellular cytotoxicity (ADCC) associate with decreased mother-to-child-transmission and correlate with improved outcomes in infected infants.

**Methods:** ADCC responses were assessed using an infection-based luciferase assay in maternal and infant samples against viruses incorporating HIV-1 envelopes isolated from the chronically infected mothers. Human Isotyping Multiplex assays were used to quantify the magnitude of IgG present in the samples. Differences, correlations, and outcomes among transmitting (TM) versus non-transmitting mothers (NTM) and among HIV infected (HI) as compared to HIV exposed uninfected (HEU) infants were assessed using Wilcoxon rank-sum test, Spearman correlation, and Kaplan Meier analysis.

**Results:** Breastfeeding, Antiretroviral, and Nutrition (BAN) cohort samples were obtained from 13 mother infant dyads around 40 days prior to documented transmission and from 23 pairs without transmission at a similar time after birth. TMs and NTMs had similar plasma virus levels ( $p=0.63$ ) and absolute CD4 count ( $p=0.95$ ), and HI and HEU infants had similar birthweight ( $p=0.34$ ). HEU infants had higher ADCC responses compared to matched HI infants ( $p=0.05$ ). NTM as compared to TM also had higher plasma ADCC responses although the difference was not statistically significant ( $p=0.15$ ). HI infants with low ADCC responses (below the median for HI group) had more serious adverse events compared to those with high ADCC responses (hazard ratio, 7.33; 95% confidence interval, 1.17 to 45.94;  $p=0.03$ ). Infant and maternal ADCC was highly correlated ( $\rho=0.53$ ,  $p=0.001$ ), and the magnitude of the responses decreased in the infants over time ( $\rho=-0.57$ ,  $p=0.0003$ ). ADCC and nAb responses were not correlated in the infants ( $\rho=0.19$ ,  $p=0.37$ ) or the mothers ( $\rho=0.28$ ,  $p=0.15$ ). There was no significant difference in the magnitude of IgG between TM and NTM ( $p=0.54$ ) or HI versus HEU ( $p=0.21$ ), and IgG levels did not correlate with ADCC activity in maternal ( $p=0.25$ ) or infant ( $p=0.48$ ) plasma.

**Conclusion:** Higher infant ADCC and not nAb responses against strains circulating in their infected mother correlate with both decreased breast milk mother-to-child-transmission and lower infant morbidity. Additionally, the quality not quantity of IgG is important for these ADCC responses.

**600 DOLUTEGRAVIR AND VIRAL LOAD SUPPRESSION AMONG PEDIATRIC PATIENTS IN CARE IN ZAMBIA**

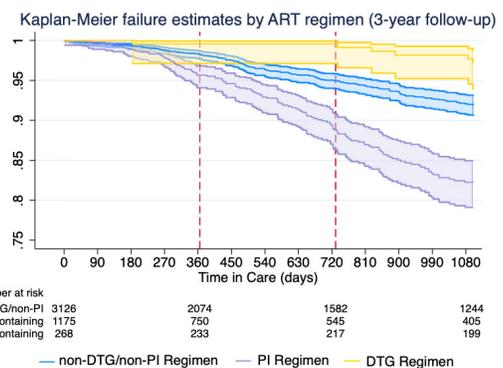
**Shilpa S. Iyer**<sup>1</sup>, Jake Pry<sup>2</sup>, Godwin Nyirenda<sup>2</sup>, Mwansa Lumpa<sup>2</sup>, Carolyn Bolton<sup>1</sup>, Michael E. Herce<sup>2</sup>, Kevin M. Zambia<sup>3</sup>, Mwangelwa Mubiana-Mbewe<sup>2</sup>  
<sup>1</sup>University of Alabama at Birmingham—CIDRZ, Lusaka, Zambia, <sup>2</sup>Centre for Infectious Disease Research in Zambia, Lusaka, Zambia, <sup>3</sup>Ministry of Health, Lusaka, Zambia

**Background:** Preliminary results from the ODYSSEY trial led to FDA approval for the use of Dolutegravir (DTG) in treatment-naïve or experienced young children. Previous research, predominately in well-resourced settings, has demonstrated improved efficacy, tolerability and durability of DTG when compared to other first-line antiretroviral therapy (ART) regimens. Here we assess viral suppression among pediatric patients  $\leq 18$  who received a DTG-based ART regimen in Lusaka, Zambia.

**Methods:** We reviewed a cohort of HIV+ individuals aged  $\leq 18$  years with recorded HIV care visit between January 1, 2019 and December 31, 2019 in five health facilities in Lusaka, Zambia. Routine programmatic data, including demographic, clinical, and laboratory measures were extracted from electronic medical records. The outcome, viral load non-suppression, (viremic), was defined as a viral load  $>1,000$  copies/ml. We created a fixed-effects regression model and Kaplan-Meier curves using Stata IC 15.1.

**Results:** A total of 2245 individuals with a median age of 8 years were included in the analysis. Median time from HIV diagnosis to ART initiation was 14 days (IQR: 0-56 days). ART initiation between 10-14 years is associated with 2.7 ( $p=0.017$ ) times the odds of being viremic compared to individuals aged 15-18 years. ART regimen was found to be significantly associated with viremia, with those on regimens containing protease inhibitors (PI) having significantly higher odds of viremia compared to those on non-PI/non-DTG regimens (OR: 2.13,  $p$ -value:  $<0.001$ ). Remarkably, DTG-containing regimens were associated with significantly lower odds of viremia compared to those on non-PI/non-DTG regimens (OR=0.15,  $p<0.001$ ). Survival analysis show significantly lower cumulative incidence estimates of viremia among those on DTG-containing regimens compared to non-DTG/PI-containing regimens at three years of follow-up (log-rank:  $<0.001$ ) (Fig. 1). Objective assessments of ART adherence were not available in this dataset to distinguish between improved efficacy and tolerability.

**Conclusion:** DTG-associated regimens were associated with superior viral suppression among children living with HIV in Zambia, supporting their inclusion in the national guidelines for all eligible pediatric clients. The lack of an objective ART adherence tool is a limitation of this study. Improved fidelity of DTG-containing pediatric ART regimens are likely to attain sustained viral suppression and improved health outcomes.



**601 SWITCHING EFAVIRENZ TO RILPIVIRINE IN VIROLOGICALLY SUPPRESSED ADOLESCENTS WITH HIV**

**Wanatpreeya Phongsamart**<sup>1</sup>, Watsamon Jantarabenjakul<sup>2</sup>, Sasitorn Chantaratin<sup>1</sup>, Supavorn Anugulruengkitt<sup>2</sup>, Piyarat Suntarattiwong<sup>3</sup>, Pope Kosalaraksa<sup>4</sup>, Alan Maleesatharn<sup>1</sup>, Kulkanya Choekphaibulkit<sup>1</sup>

<sup>1</sup>Mahidol University, Bangkok, Thailand, <sup>2</sup>Chulalongkorn University, Bangkok, Thailand, <sup>3</sup>Queen Sirikit National Institute of Child Health, Bangkok, Thailand, <sup>4</sup>Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

**Background:** Efavirenz (EFV) based-antiretroviral therapy (ART) is commonly used for first-line treatment in adolescents and children with HIV but is associated with neuropsychiatric and metabolic side effects. Rilpivirine

(RPV) has a more favorable tolerability profile and switching EFV to RPV in virologically suppressed adults was safe and efficacious, but data in adolescents are limited.

**Methods:** Open-label, single-arm, study in adolescents aged 12-18 years old receiving EFV plus two NRTIs for >3 months with virologic suppression. Efavirenz was switched to a RPV 25 mg tablet once daily. HIV-1 RNA viral load, CD4 cell counts, fasting total cholesterol, triglyceride, and glucose were assessed over 48 weeks. Neuropsychiatric adverse events, depression and quality of life (QOL) were also evaluated.

**Results:** 102 (52% male) adolescents were enrolled. Median age at entry was 15 years with a nadir CD4 count of 288 cells/mm<sup>3</sup> (12.2%), with 58% receiving TDF/FTC. At week 48, 94 of 102 subjects (92.2%) maintained virologic suppression, with no significant change in CD4 counts. Six subjects had virologic failure, 2 had RPV-associated mutations (K101E and Y181C). Significant decreases in total cholesterol, triglyceride, HDL and LDL ( $p < 0.001$ ) occurred at weeks 24 and 48. No significant changes in EFV-related symptoms, health-related QOL and depression score were observed; although there was significant improvement in performance-based assessments of executive function at week 24.

**Conclusion:** More than 90% of adolescents switching from EFV- to RPV maintained virologic suppression after 48 weeks. RPV was well tolerated and associated with improvements in metabolic profiles, executive and cognitive function.

## 602 MINDFULNESS TO IMPROVE ART ADHERENCE AND ACCEPTANCE IN YOUTH LIVING WITH HIV: AN RCT

Erica Sibinga<sup>1</sup>, Lindsey Webb<sup>2</sup>, Deanna Kerrigan<sup>3</sup>, Vicki Tepper<sup>4</sup>

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins School of Public Health, Baltimore, MD, USA, <sup>3</sup>George Washington University, Washington, DC, USA, <sup>4</sup>University of Maryland, Baltimore, MD, USA

**Background:** Individuals 13-24 years old make up an alarming and disproportionate 21% of new HIV diagnoses. Unfortunately, this age group is less engaged in care and only half as likely to achieve HIV viral suppression (seen in only 30%) than older individuals, leading to significant vulnerability to illness and limiting broader efforts to end the HIV epidemic

**Methods:** Our previous research found that mindfulness programming for HIV-infected youth was promising, showing improved coping, life satisfaction, and potentially decreased HIV viral load. This NIH-funded RCT aimed to further explore the effect of evidence-based mindfulness-based stress reduction (MBSR) vs. health education control (HT) on HIV medication adherence in HIV-infected youth. Data were collected at baseline, 3, 6, and 12 months. Generalized linear additive modeling was conducted to determine differences by arm over time. In-depth interviews were conducted with 20 individuals from both study arms at baseline and follow-up.

**Results:** Seventy-four 13-24 year old participants from medical clinics at two major academic centers completed baseline data collection and were randomized to MBSR or HT. Following program participation, MBSR participants had greater increases in medication adherence ( $p = 0.001$ ) and greater decline in HIV viral load ( $p = 0.052$ ) at 3-month follow-up, but not at 6 or 12 months. Qualitative data describe challenges of managing HIV as a stigmatized, chronic condition, amidst significant stressors and social inequalities. MBSR participants perceived program benefit related to social support and to their enhanced capacity to non-judgmentally observe and accept difficult thoughts, feelings, and experiences associated with living with HIV, which they believe facilitated greater medication adherence.

**Conclusion:** This mixed-methods RCT finds that MBSR participants had larger increase in self-reported medication adherence and reduction in HIV viral load following program participation, but not at follow-up. Also, MBSR participants perceive greater capacity for acceptance of the complex and difficult thoughts and emotions related to living with HIV, leading to improved medication adherence. Given the significant vulnerability of this population and the importance of achieving higher rates of HIV viral suppression to decrease transmission and end the HIV epidemic, MBSR remains a promising approach to enhance the treatment of HIV-infected youth and young adults.

603



## RANDOMIZED CONTROLLED TRIAL OF AN ADHERENCE INTERVENTION IN YOUTH LIVING WITH HIV

K. Rivet Amico<sup>1</sup>, Jane C. Lindsey<sup>2</sup>, Michael Hudgens<sup>3</sup>, Ronald Dallas<sup>4</sup>, Keith J. Horvath<sup>5</sup>, Amanda R. Dunlap<sup>1</sup>, Rachel Goolsby<sup>3</sup>, Megan Mueller Johnson<sup>1</sup>, Barbara Heckman<sup>6</sup>, Jessica R. Crawford<sup>1</sup>, Elizabeth Secord<sup>7</sup>, Murlu Purswani<sup>8</sup>, Daniel Reiden<sup>9</sup>, Aditya Gaur<sup>10</sup>, for the ATN 152 TERA Study Team

<sup>1</sup>University of Michigan, Ann Arbor, MI, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>4</sup>St. Jude Children's Research Hospital, Memphis, TN, USA, <sup>5</sup>San Diego State University, San Diego, USA, <sup>6</sup>Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA, <sup>7</sup>Wayne State University, Detroit, MI, USA, <sup>8</sup>Bronx-Lebanon Hospital Center, Bronx, NY, USA, <sup>9</sup>University of Colorado Denver, Denver, CO, USA, <sup>10</sup>St. Jude Children's Research Hospital, Memphis, TN, USA

**Background:** Youth living with HIV (YLWH) have low rates of viral suppression (VS). We evaluated the impact of a 12-week intervention using remote coaching, electronic dose monitoring (EDM) and tailored outreach (the Triggered Escalating Real-Time Adherence [TERA] intervention) compared to standard of care (SOC) on VS and electronic dose monitored adherence of antiretroviral therapy (ART), among wiremic (HIV-1 RNA  $\geq 200$  copies/ml) youth (ages 13-24 yrs) in the United States.

**Methods:** 89 YLWH were randomized to TERA intervention versus SOC and followed for 48 weeks with study visits at weeks 0, 4, 12, 24, 36 and 48. Remote coaching sessions were delivered at Weeks 0, 4 and 12, with continuous EDM monitoring for delayed or missed ART doses and as needed outreach from coach by text and phone in the TERA arm. Primary outcome was VS at week 12 (HIV-1 RNA <200 cp/ml at 10-14 weeks). RNA  $\geq 200$  cp/ml (10-14 wks) or missing set to failure. Proportions with VS were compared by arm (Fisher's exact test and log binomial regression for adjusted comparisons). Secondary outcomes included EDM adherence summarized in 12-week intervals using percent days device was opened (PCT12) and incidence rates (IR) of number of  $\geq 7$ -day gaps between openings (GAPIR), compared using Wilcoxon rank sum tests. Results are reported using data collected before the study paused due to COVID-19 in March 2020.

**Results:** 88 YLWH completed study entry: 55% male, 85% Black/African American, median age 22 (range 13-24 yrs), 44% acquired HIV perinatally and 30% on  $\geq 3$ rd ART regimen. VS was achieved in 15/43 (35%; 95% CI: 21%, 51%) TERA arm and 16/45 (36%; 95% CI: 22%, 51%) SOC arm participants; difference (TERA-SOC) was -1% (95% CI: -21%, 20%). No differences by arm were apparent at weeks 24, 36 or 48 or after adjusting for sex, age or mode of transmission. Of 54 participants with opportunity for follow-up to week 48, 14% (4/29) and 8% (2/25) in the TERA and SOC arms, respectively, achieved consistent VS (TERA - SOC: 6%; 95% CI: 15%, 25%). Median (Q1, Q3) PCT12 over the first 12 weeks was 72% (47%, 89%) versus 41% (21%, 59%) in the TERA and SOC arms, respectively ( $p < 0.001$ ). GAPIRs were higher in the SOC arm than TERA arm with SOC/TERA IR ratio of 2.51 (95% CI: 1.90, 3.33).

**Conclusion:** The 12-week TERA intervention improved adherence to ART but not VS among YLWH failing treatment. TERA will be further assessed for indication, timing, and outcome duration in YLWH.

## 604 IMPAACT 2014 24-WEEK PK AND SAFETY OF DORAVIRINE/3TC/TDF IN ADOLESCENTS WITH HIV-1

Ann J. Melvin<sup>1</sup>, Brookie Best<sup>2</sup>, Petronella Muresan<sup>3</sup>, Sarah Pasyar<sup>3</sup>, Hedy Tepler<sup>4</sup>, Kelly Yee<sup>4</sup>, Katie McCarthy<sup>5</sup>, Rachel Schecter<sup>5</sup>, Hong Wan<sup>4</sup>, Lina De Montigny<sup>4</sup>, Linda Aurpibul<sup>6</sup>, Pradthana Ounchanum<sup>7</sup>, Avy Violaris<sup>8</sup>, Nicole Tobin<sup>9</sup>, Ellen Townley<sup>10</sup>

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>University of California San Diego, San Diego, CA, USA, <sup>3</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>4</sup>Merck & Co, Inc, Kenilworth, NJ, USA, <sup>5</sup>FHI 360, Durham, NC, USA, <sup>6</sup>Chiang Mai University, Chiang Mai, Thailand, <sup>7</sup>Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand, <sup>8</sup>University of the Witwatersrand, Johannesburg, South Africa, <sup>9</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>10</sup>National Institutes of Health, Rockville, MD, USA

**Background:** Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) active against both wild-type HIV-1 and the most common NNRTI-resistant variants. DOR, alone or as a fixed dose combination (FDC) of DOR/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF), is approved for treatment in antiretroviral-naïve and virologically-suppressed adults with HIV-1 infection. IMPAACT 2014 investigated the pharmacokinetics (PK) and safety of DOR as a component of the FDC in adolescents with HIV-1 through 24 weeks. The

100mg dose of DOR evaluated in this study was previously confirmed based on 2-week safety and single dose PK in adolescents >45kg.

**Methods:** Adolescents with HIV-1, between the ages of 12 and 18 years and weighing at least 45 kg who were antiretroviral therapy (ART)-naïve or virologically-suppressed on stable ART, were enrolled into an open-label trial evaluating the once daily FDC tablet regimen of DOR 100mg, 3TC 300mg, and TDF 300mg. Safety, virologic and PK data were evaluated through Week 24 of therapy.

**Results:** Forty-five adolescents (43 virologically-suppressed on stable ART and 2 ART-naïve at enrollment) were evaluated. Mean age of the participants was 15 years (range 12-17 years) with a mean weight of 53.8 kg (range 45.1 – 79.8 kg). Overall, the FDC of DOR/3TC/TDF was well tolerated through 24 weeks. There was a low incidence of drug-related AEs (2.2% with 95% CI [0.1-11.8]), no drug-related SAEs or AEs  $\geq$ Grade 3 and no treatment discontinuation due to AEs. In the virologically-suppressed on stable ART participants there were no protocol-defined virologic failures and HIV-1 RNA <50 copies/mL was maintained at 95.3% with a 95% CI [84.2, 99.4]. One of the 2 ART-naïve participants achieved virologic suppression by Week 24 and the other experienced protocol-defined virologic failure related to adherence issues. DOR geometric mean steady state trough concentration at Week 4 was 747 nM and subsequent concentrations were above the lower efficacy bound (>560 nM) for adults with HIV receiving 100mg QD DOR. PK for 3TC and TFV from the FDC were consistent with reported PK in adults receiving each drug individually.

**Conclusion:** At Week 24 the PK, safety, and tolerability of DOR as an FDC of DOR/3TC/TDF in adolescents were comparable to data reported in adults. Overall virologic efficacy in the trial showed favorable antiretroviral effect comparable to data reported in adults.

## 605 ABACAVIR DOSING IN NEONATES FROM BIRTH: A PHARMACOKINETIC ANALYSIS

**Adrie Bekker**<sup>1</sup>, Edmund Capparelli<sup>2</sup>, Avy Violari<sup>3</sup>, Mark F. Cotton<sup>1</sup>, Ruth Mathiba<sup>3</sup>, Andrew A. Wiznia<sup>4</sup>, Renee Browning<sup>5</sup>, Jack Moyer<sup>6</sup>, Bobbie Graham<sup>7</sup>, Eric Deddoet<sup>1</sup>, Helena Rabie<sup>1</sup>, Mark Mirochnick<sup>8</sup>, Tim R. Cressley<sup>9</sup>, for the IMPAACT P1106 Team  
<sup>1</sup>Family Center for Research with Ubuntu, Stellenbosch University, Cape Town, South Africa, <sup>2</sup>University of California San Diego, San Diego, CA, USA, <sup>3</sup>Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa, <sup>4</sup>Jacobi Medical Center, New York, NY, USA, <sup>5</sup>Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA, <sup>6</sup>Division of Extramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA, <sup>7</sup>Frontier Science Foundation, Amherst, NY, USA, <sup>8</sup>Boston University School of Medicine, Boston, MA, USA, <sup>9</sup>PHPT/IRD 174, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand

**Background:** Antiretroviral treatment (ART) from birth in neonates (<28 days of age) at high risk of HIV acquisition can provide both enhanced HIV prophylaxis and early treatment. Although abacavir (ABC) is a recommended component of 1st line ART in children, pharmacokinetic (PK) data and dosing information are limited for neonates. ABC is licensed for children >3 months of age (8 mg/kg, BID), while the WHO recommends weight band dosing for children  $\geq$ 4 weeks weighing  $\geq$ 3 to <5.9 kg (60 mg or ~ 10 – 20 mg/kg, BID). We performed a PK analysis using ABC plasma concentrations from neonates and young infants to determine ABC dosing for term neonates.

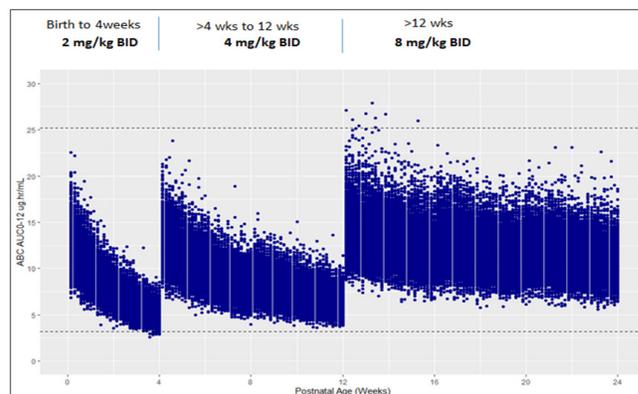
**Methods:** Data were pooled from 3 studies administering ABC liquid: (1) PACTG 321 (2) a Tygerberg cohort and (3) IMPAACT P1106. Studies 1 and 2 performed intensive PK sampling in term neonates receiving ABC for HIV prophylaxis. Study 3 performed sparse PK sampling on term and low birth weight (LBW; <2500g) infants with HIV initiating ABC based ART after 1 month of life. ABC PK parameters were estimated using a population approach. Monte Carlo simulations were run for virtual term neonates to achieve ABC exposures (AUC<sub>0-12</sub>) within the expected range based on WHO weight band dosing (3.2 to 25.2 mcg.hr/mL).

**Results:** Forty-five infants contributed 308 ABC concentrations; 21 term neonates <15 days of life undergoing intensive PK sampling. LBW infants were older at first PK assessment with a median (range) postnatal age (PNA) of 78 (41–190) days and weight of 3.6 (2.4–5.8) kg. ABC plasma concentrations were described by a 1-compartment model. ABC CL/F was allometrically scaled according to infant body weight and PNA described maturation in a non-linear manner. At birth, term neonates demonstrated a low ABC CL/F of 0.15 L/hr/kg reaching 0.71 L/hr/kg by 6 months of age (~five-fold increase). ABC CL/F in LBW

infants at 6 weeks PNA was similar to term infants of a similar chronological age. Simulations predicted that an ABC dose of 2 mg/kg BID in term neonates and then 4 mg/kg BID from 4–12 weeks of age, achieved an AUC<sub>0-12</sub> in the expected range (Fig 1).

**Conclusion:** ABC elimination is greatly reduced at birth but rapidly increases over the first weeks of life. Our proposed mg/kg dosing for ABC from birth to 3 months of life provides exposures within the expected range, but data on LBW infants are needed. Using the WHO weight band dose of 60 mg for children  $\geq$ 4 weeks and weighing  $\geq$ 3 to <5.9 kg would lead to higher exposures, but no safety concerns have been reported.

**Figure 1:** Predicted abacavir exposure (AUC<sub>0,12</sub>) from birth to 24 weeks of age for a 3 kg term neonate when ABC is administered at the proposed dose (90,000 infants were simulated across the age range)



## 606 DOSE OPTIMISATION OF LONG-ACTING INJECTABLES IN NEONATES VIA PBPK MODELLING

**Fazila S. Bunglawala**<sup>1</sup>, Nicolas Cottura<sup>1</sup>, Maiara C. Montanha<sup>1</sup>, Hannah Kinvig<sup>1</sup>, Edmund Capparelli<sup>2</sup>, Mark Mirochnick<sup>3</sup>, Marco Siccardi<sup>1</sup>  
<sup>1</sup>University of Liverpool, Liverpool, UK, <sup>2</sup>University of California San Diego, San Diego, CA, USA, <sup>3</sup>Boston University, Boston, MA, USA

**Background:** As we move towards the use of LA injectables for HIV treatment & prevention, there is great interest in the potential of these formulations for neonates & children. However, clinical trials in paediatric patients, especially neonates, are often impeded by logistical & ethical barriers. PBPK modelling can be applied to inform the selection of new therapeutics at appropriate doses. The objective of this study was to evaluate intramuscular (IM) & oral CAB in neonates & identify an appropriate initial dosing regimen to rapidly achieve therapeutic levels using mechanistic PBPK modelling.

**Methods:** A previously published whole-body neonatal PBPK model was modified to simulate CAB in neonates. The ontogeny of the key enzyme UGT1A1 was refined and validated using observed neonatal raltegravir clinical data. For further validation of model input parameters, IM & oral CAB were simulated in an adult PBPK model; observed, adult clinical data were used for comparison. Since depot release in the neonate is unknown, simulations were performed using the adult release rate ( $4.5 \times 10^{-4}$ ) as well as with this parameter decreased & increased by 2, 5 and 10-fold. The possibility of an oral safety lead-in in conjunction with an IM injection was also explored in the model.

**Results:** Several scenarios were modelled in healthy neonates with the aim of achieving plasma exposures 4-fold above the reported protein adjusted (PA) IC90 ( $4 \times \text{PAIC}_{90}$ : 0.664 ug/mL). Early CAB concentrations & time to achieve target concentrations were sensitive to the IM release rate. The initial simulations of IM CAB suggested that a delay of 35 hours (Regimen 1, Table 1) is required to reach target concentrations if the infant CAB release rate is identical to adults. To overcome this lag a single dose oral lead-in of CAB was simulated (Regimen 8, Table 1).

**Conclusion:** Though long-acting formulations have many advantages their utility in special populations such as neonates is still in question. This study evaluated the pharmacology of injectable IM CAB in neonates. Assuming the CAB depot release rate in neonates is the same as observed in adults, our simulations suggest a 20mg (4.4–6.7 mg/kg) IM injection alongside a single dose of oral CAB both initiated on day 0, is suitable to achieve target exposure ( $>4 \times \text{PAIC}_{90}$ ). However, since the effect of neonatal physiology on the depot release rate is unknown, observational data are needed to delineate the depot

release rate in neonates and establish an appropriate neonatal CAB dosing regimen.

Table 1 Summary of PK parameters of oral and IM CAB in neonates

| Regimen | Dose  | Release rate | Lag time to plasma concentration $\geq 4^* \text{PAIC}_{50}$ (h) | C <sub>max</sub> (mg/L) | C <sub>trough</sub> (mg/L) | AUC <sub>0-28d</sub> (mg* <sup>h</sup> /L) | AUC <sub>av</sub> (mg* <sup>h</sup> /L) |
|---------|---|--------------|--|-------------------------|----------------------------|--|---|
| 1       | Single 20 mg IM CAB on Day 0                        | Adult*       | 35   | 2.55                    | 1.20                       | 1218.2                                     | 43.5                                    |
| 2       | Single 20 mg IM CAB on Day 0                        | 0.1x Adult   | -  | 0.28                    | 0.15                       | 134.9                                      | 4.8                                     |
| 3       | Single 20 mg IM CAB on Day 0                        | 0.2x Adult   | -  | 0.53                    | 0.28                       | 260.5                                      | 9.3                                     |
| 4       | Single 20 mg IM CAB on Day 0                        | 0.5x Adult   | 77   | 1.33                    | 0.70                       | 646.6                                      | 23.1                                    |
| 5       | Single 20 mg IM CAB on Day 0                        | 2x Adult     | 17   | 4.69                    | 1.80                       | 2150.6                                     | 76.8                                    |
| 6       | Single 20 mg IM CAB on Day 0                        | 5x Adult     | 7  | 10.06                   | 2.21                       | 4176.7                                     | 149.2                                   |
| 7       | Single 20 mg IM CAB on Day 0                        | 10x Adult    | 4  | 15.85                   | 1.90                       | 5923.4                                     | 211.6                                   |
| 8       | Single 20 mg IM CAB & Single 0.8 mg PO CAB on Day 0 | Adult        | 4  | 4.69                    | 1.08                       | 1438.5                                     | 51.4                                    |

\*Adult release rate = 4.5x 10<sup>-4</sup>; <sup>4</sup>PAIC<sub>50</sub>: 0.664 mg/mL; C<sub>max</sub>, maximum plasma concentration; C<sub>trough</sub>, minimum plasma concentration; AUC<sub>0-28d</sub>, area under the curve over 28-days; AUC<sub>av</sub>, average daily area under curve over 28-day simulations.

**607 OPTIMIZING DOLUTEGRAVIR INITIATION IN NEONATES USING POPULATION PHARMACOKINETIC MODEL**

Joseph Piscitelli<sup>1</sup>, Mina Nikanjam<sup>1</sup>, Jeremiah Momper<sup>1</sup>, Brookie Best<sup>1</sup>, Edward Acosta<sup>2</sup>, Mark Mirochnick<sup>3</sup>, Diana F. Clarke<sup>4</sup>, Edmund Capparelli<sup>1</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>3</sup>Boston University, Boston, MA, USA, <sup>4</sup>Boston Medical Center, Boston, MA, USA

**Background:** Dolutegravir (DTG) is a commonly used ARV in pregnant women with HIV. Limited data are available on the pharmacokinetics of placentally-acquired DTG in infants born to mothers receiving DTG. For infants exposed to HIV, optimized DTG dosing during the first days of life may depend upon (i) the time of the last maternal dose prior to delivery and (ii) the time of DTG initiation after birth. The current study utilized population pharmacokinetic (popPK) modeling and simulation to optimize initiation of DTG in neonates.

**Methods:** IMPAACT P1026S evaluated DTG PK during pregnancy (2nd, 3rd trimester) and post-partum in patients receiving 50mg daily. Paired cord blood and maternal concentrations at delivery along with neonatal washout concentrations were collected. Maternal data were combined in a popPK model. The infant elimination half-life was estimated from neonatal washout PK data. Monte Carlo simulations were utilized to generate maternal DTG concentrations at delivery (last maternal dose 6, 12, and 24 hr prior to delivery) in 3000 virtual mother-infant pairs. Paired cord blood to maternal plasma ratios were used to estimate neonatal DTG concentrations at birth and an additional sequential simulation performed to estimate neonatal pre-dose and C<sub>max</sub> concentrations following a 5 mg dose administered 0, 24, 48, or 72 hr after birth.

**Results:** Thirty-one maternal subjects and 18 neonates contributed data to the analysis. A total of 552 maternal concentrations were utilized to develop the maternal popPK model. The median apparent clearance (CL/F) in the third trimester was 1.06L/hr, 40% higher than post-partum. Seventy infant washout samples were utilized for the neonatal popPK model. The estimated half-life was 44.1hr. The median ratio of cord blood to maternal plasma concentrations at delivery was 1.25 (1.07 – 1.40 [IQR]). The maternal and neonatal popPK models were utilized in sequential simulations and are summarized in Table 1.

**Conclusion:** Neonatal DTG concentrations at birth varied considerably based on the time of last maternal dose prior to delivery and exhibited a slow decline over the first few days of life. Initiating infant DTG at 24–48 hrs after birth is appropriate when the last maternal dose was given within 24 hours of delivery. PopPK modeling and simulation can help evaluate neonatal DTG concentrations and dosing regimens to guide future clinical trials.

Table 1. Median Infant Concentration Pre and Post 5mg Dose

| Maternal Time from Last Dose to Delivery (hours) | Infant Time after Birth to 5 mg Dose (hours)  |      |      |      |
|--|---|------|------|------|
|  | At Birth                                      | 24   | 48   | 72   |
|  | Infant Median Pre-dose Concentration (mcg/mL) |      |      |      |
| 6  | 3.42  | 2.20 | 1.48 | 1.04 |
| 12   | 2.37  | 1.63 | 1.01 | 0.74 |
| 24   | 1.06  | 0.78 | 0.50 | 0.33 |
|  | Infant Median C <sub>max</sub> (mcg/mL)       |      |      |      |
| 6  | 8.11  | 6.92 | 6.24 | 5.81 |
| 12   | 7.10  | 6.36 | 5.79 | 5.53 |
| 24   | 5.85  | 5.56 | 5.30 | 5.15 |

**608 POPULATION PHARMACOKINETICS OF VRC01LS IN TERM INFANTS AND ADULTS**

Jincheng Yang<sup>1</sup>, Coleen K. Cunningham<sup>2</sup>, Elizabeth J. McFarland<sup>3</sup>, John R. Mascola<sup>4</sup>, Barney S. Graham<sup>5</sup>, Julie E. Ledgerwood<sup>6</sup>, Richard A. Koup<sup>5</sup>, Emily E. Coates<sup>5</sup>, Katherine V. Houser<sup>5</sup>, Lucio Gama<sup>4</sup>, Martin R. Gaudinski<sup>4</sup>, Petronella Muresan<sup>6</sup>, Charlotte Perlowski<sup>7</sup>, Edmund Capparelli<sup>1</sup>

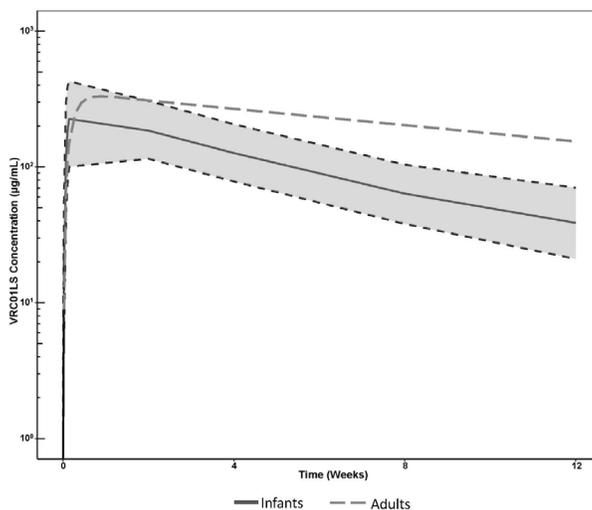
<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>Duke University School of Medicine, Durham, NC, USA, <sup>3</sup>University of Colorado, Aurora, CO, USA, <sup>4</sup>National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, <sup>5</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>6</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>7</sup>FHI 360, Durham, NC, USA

**Background:** VRC01LS, a long-acting variant of VRC01, is a broadly neutralizing monoclonal antibody (bNAbs) with activity against many HIV-1 strains. The increased half-life from the 2 amino acid modifications in the native Fc region of the VRC01 antibody makes VRC01LS a desirable candidate for use as infant prophylaxis and treatment. The current study aimed to develop a composite VRC01LS population pharmacokinetic (PopPK) model in infants and adults to help optimize infant VRC01LS dosing.

**Methods:** VRC01LS PK data were pooled from two separate studies: HIV-exposed infants (IMPACT P1112, N= 21) and healthy adults (VRC606, N= 49). All infants received a dose of VRC01LS subcutaneously (SC) using weight-band dosing (<4.5kg: 80 mg; ≥4.5kg: 100 mg) within the first 4 days of life. Breast-fed infants also received a 2nd dose at week 12. Adults received 1 or 3 doses of VRC01LS at 5–40mg/kg IV or 5 mg/kg SC. A total of 907 VRC01LS concentrations were analyzed using NONMEM version 7.3, FOCEI method. Allometric scaling was incorporated into the PopPK model before evaluation of other potential covariates. Age group (infants vs. adults), gender, dose (mg/kg), dose number (1st vs 2nd/3rd Dose), creatinine and hematocrit were evaluated as potential covariates. A Monte Carlo simulation (n=1000) was performed using the final model to predict (median, 95% CI) infant VRC01LS concentrations following SC administration.

**Results:** A two-compartment model best describes the data. The key PopPK parameters are: Clearance (CL, L/h/70kg) = 0.00148\*(WT/70)<sup>0.85</sup> Volume at Steady State (V<sub>ss</sub>, L/70kg) = 3.53\*(WT/70) \*0.829 (if 2nd/3rd Dose) Rate of Absorption (KA, 1/h) = 0.0129\*2.78 (if infant) Bioavailability (F, %) = 63.8\*0.714 (if infant) Between-subject variabilities are 27% for CL and 24% for V<sub>ss</sub>. Infants have lower bioavailability and more rapid absorption than adults. VRC01LS CL/F in infants is confounded by the "dilutional" effect of infant growth; mean weight increased from 3.0kg at birth to 5.7kg at week 12. Infant VRC01LS CL/F is lower than previously reported for VRC01 (Li CPT 2020). Monte Carlo simulations of 80mg in infants shortly after birth predicts a median week 12 concentration of 34.5mcg/mL with 9.8% of VRC01LS concentrations ≥ 50mcg/mL and 96.3% of VRC01LS concentrations ≥ 20mcg/mL.

**Conclusion:** The PopPK of VRC01LS demonstrates slow elimination in infants and adults allowing every 12 week dosing. VRC01LS has promise in infant HIV prophylaxis and treatment.



**609 SAFETY AND PHARMACOKINETICS OF VRC01LS AND 10-1074 AMONG CHILDREN IN BOTSWANA**

**Edmund Capparelli**<sup>1</sup>, Gbolahan Ajibola<sup>2</sup>, Kenneth Maswabi<sup>2</sup>, Molly Pretorius Holme<sup>3</sup>, Kara Bennett<sup>4</sup>, Kathleen M. Powis<sup>5</sup>, Kelly E. Seaton<sup>6</sup>, Adrian McDermott<sup>7</sup>, Marina Caskey<sup>8</sup>, Lucio Gama<sup>7</sup>, Patrick Jean-Philippe<sup>9</sup>, Joseph Makhema<sup>2</sup>, Daniel R. Kuritzkes<sup>10</sup>, Mathias Lichtenfeld<sup>11</sup>, Roger Shapiro<sup>3</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>3</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>4</sup>Bennett Statistical Consulting Inc, Ballston Lake, NY, USA, <sup>5</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>6</sup>Duke University, Durham, NC, USA, <sup>7</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>8</sup>The Rockefeller University, New York, NY, USA, <sup>9</sup>National Institute of Allergy and Infectious Diseases, Rockville, MD, USA, <sup>10</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>11</sup>Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA

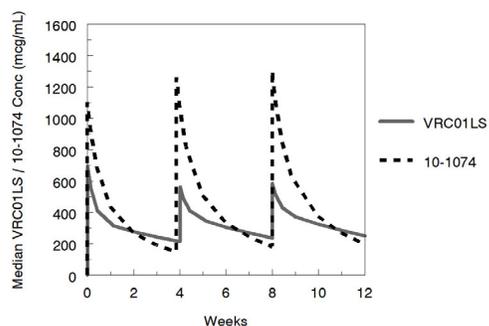
**Background:** Broadly neutralizing monoclonal antibodies (bNAbs) suppress HIV-1 RNA and may deplete viral reservoir. Before evaluating dual bNAbs as a treatment alternative in children, we evaluated the safety and pharmacokinetics (PK) of intravenous VRC01LS and 10-1074 in early-treated children with HIV on suppressive antiretroviral treatment (ART).

**Methods:** Eligible children had received ART from <7 days through ≥96 weeks of life, and had HIV-1 RNA <40 copies/mL for ≥24 weeks prior to enrollment. The initial PK phase (A) (previously presented) evaluated safety and PK of each bNAb separately in two groups of 6 participants for 12 weeks. In the second phase (B), we evaluated safety and PK of the two bNAbs in combination, and with a higher VRC01LS maintenance dose based on review of Phase A. Six participants received IV infusions every 4 weeks of both 10-1074 (30 mg/kg) and VRC01LS (30mg/kg first dose followed by 15mg/kg maintenance). PK samples were collected over 8 weeks and safety evaluated through 32 weeks. PK concentrations were measured by ELISA. Results were combined from both phases for analysis by noncompartmental (first dose C<sub>max</sub>, Cave and trough) and population PK (PopPK) methods. For the PopPK analysis, a two-compartment model was developed for each bNAb using NONMEM and 5000 virtual participants were simulated to predict steady-state concentrations.

**Results:** There were no infusion reactions, no expedited adverse events, and no grade 3 or 4 events related to dual bNAb administration through 32 weeks. The first dose median (range) C<sub>max</sub> and trough for VRC01LS were 776 (559-846) mcg/mL and 230 (158-294) mcg/mL, and first dose median (range) C<sub>max</sub> and trough for 10-1074 were 1405 (876-1999) mcg/mL and 133 (84-319) mcg/mL. All participants' average concentrations following the first dose were >245 mcg/mL for VRC01LS and 290 mcg/mL for 10-1074. The population t<sub>1/2</sub> was 38 days for VRC01LS and 16 days for 10-1074; in contrast, VRC01LS t<sub>1/2</sub> in healthy adults has previously been reported as 71 days (Gaudiniski 2018). VRC01LS and 10-1074 elimination were similar when administered alone or in combination. The predicted median steady-state troughs with Phase B dosing were 269 mcg/mL (VRC01LS) and 211 mcg/mL (10-1074).

**Conclusion:** IV infusions of VRC01LS and 10-1074 were well tolerated as dual therapy in children, and generated concentrations similar to those following single bNAb administration. Monthly dosing of VRC01LS at 15mg/kg and 10-1074 at 30 mg/kg achieve target concentrations at steady state.

Figure 1. Predicted Median Steady-State bNAb Concentrations Monthly dosing of 10-1074 (30mg/kg) and VRC01LS (30mg/kg load, 15mg/kg)



**610 CANCER INCIDENCE IN HIV-POSITIVE CHILDREN: THE SAM STUDY, SOUTH AFRICA (2004-2014)**

**Natasha Abraham**<sup>1</sup>, Lukas Buetikofer<sup>2</sup>, Eliane Rohner<sup>2</sup>, Victor Olago<sup>1</sup>, Matthias Egger<sup>2</sup>, Elvira Singh<sup>1</sup>, Julia Bohlius<sup>3</sup>, Mazvita Muchengeti<sup>1</sup>

<sup>1</sup>National Health Laboratory Service, Johannesburg, South Africa, <sup>2</sup>University of Bern, Bern, Switzerland, <sup>3</sup>Swiss Tropical and Public Health Institute, Basel, Switzerland

**Background:** HIV is a known carcinogen and people living with HIV are at an increased risk for cancer compared to the general population. There is limited data available on the burden of cancer in HIV-positive children, particularly in sub-Saharan Africa. We aimed to determine cancer incidence in a national cohort of HIV-positive children (aged 0-14 years) in South Africa.

**Methods:** The South African HIV Cancer Match (SAM) study used privacy-preserving record linkages to create a national cohort of people living with HIV with cancer outcomes from national laboratory and South African National Cancer Registry data. We included children aged 0-14 years old at their first HIV-related laboratory record within the South African public sector health laboratories between 2004 and 2014 who had at least two distinct HIV-related laboratory records. We defined time under observation from the date of the first HIV-related laboratory test to cancer diagnosis or to last known HIV-related laboratory record. We calculated crude cancer incidence rates per 100,000 person-years.

**Results:** A total of 313,097 HIV-positive children were included in the study. In 802,030 person-years of follow-up, 743 incident cancers were diagnosed for an overall cancer incidence rate of 92.6/100,000 person-years. The majority (58.1%) of all diagnosed cancers were in males with an incidence rate of 111.8/100,000 person-years [Interquartile range (IQR): 101.7-122.8]. The most frequent cancer was Kaposi sarcoma (20.9%) with an incidence rate of 19.3/100,000 person-years (95% confidence interval (CI):16.5-22.6) [Table 1]. Children with CD4 counts between 50-99 cells/μl at baseline and those aged 10-14 years had the highest cancer incidence rates at 137.9/100,000 person-years (95%CI: 95.2-199.7) and 121.4/100,000 person-years (95% CI: 104.6-140.9) respectively. The median time from the first HIV-related laboratory record to a cancer diagnosis was 0.8 years [IQR: 0.07-2.94].

**Conclusion:** In countries with low HIV-prevalence, leukaemias and lymphomas are the most common childhood cancers. In our study, Kaposi sarcoma is the most common cancer in HIV-infected children, as similarly seen in adults living with HIV. The higher cancer incidence rates in children aged 10-14 years were likely due to delayed HIV diagnosis with prolonged periods of immunosuppression and exposure to other oncogenic viruses. Additional analysis to determine risk factors for cancer incidence among this age-group is needed.

|   | Person-Years at Risk | Number of Incident Cancer Cases | Cancer Incidence Rate (95% CI) |
|---|----------------------|---------------------------------|--------------------------------|
| <b>Any cancer</b>                                       | 802,030              | 743                             | 92.6 (86.2 - 99.5)             |
| <b>Sex</b>  |                      |                                 |                                |
| Male  | 386,410              | 432                             | 111.8 (101.7 - 122.8)          |
| Female  | 414,610              | 311                             | 75.0 (67.1 - 83.8)             |
| <b>Top 5 cancers</b>                                    |                      |                                 |                                |
| Kaposi sarcoma  | 801,800              | 155                             | 19.3 (16.5 - 22.6)             |
| Leukaemia   | 802,010              | 98                              | 12.2 (10.0 - 14.8)             |
| Non Hodgkin Lymphoma                                    | 801,920              | 79                              | 9.8 (7.9 - 12.2)               |
| Kidney  | 802,030              | 76                              | 9.4 (7.5 - 11.8)               |
| Burkitt lymphoma  | 801,940              | 69                              | 8.6 (6.7 - 10.8)               |
| <b>Age at first HIV-related laboratory record (yrs)</b> |                      |                                 |                                |
| 0-4   | 391,940              | 367                             | 93.6 (84.5 - 103.7)            |
| 5-9   | 268,430              | 204                             | 75.9 (66.2 - 87.1)             |
| 10-14   | 141,670              | 172                             | 121.4 (104.5 - 140.9)          |
| <b>First CD4 cell count (cells/μl)</b>                  |                      |                                 |                                |
| <50   | 29,330               | 35                              | 119.3 (85.6 - 166.1)           |
| 50-99   | 20,300               | 28                              | 137.9 (95.2 - 199.7)           |
| 100-199   | 53,000               | 51                              | 96.2 (73.1 - 126.6)            |
| 200-349   | 103,770              | 76                              | 73.2 (58.4 - 91.7)             |
| 350-499   | 110,650              | 81                              | 73.2 (58.8 - 91.0)             |
| 500-699   | 131,300              | 74                              | 56.3 (44.8 - 70.7)             |
| ≥ 700   | 343,960              | 221                             | 64.2 (56.3 - 73.3)             |
| <b>Year of first HIV-related laboratory record</b>      |                      |                                 |                                |
| 2004  | 47,230               | 41                              | 86.8 (63.9 - 117.9)            |
| 2005-2009   | 432,700              | 404                             | 93.3 (84.7 - 102.9)            |
| 2010-2014   | 322,110              | 298                             | 92.5 (82.5 - 103.6)            |

## 611 GROWTH DEFICITS ARE ASSOCIATED WITH AIRFLOW OBSTRUCTION IN PERINATALLY ACQUIRED HIV

Engi F. Attia<sup>1</sup>, Wendy Yu<sup>2</sup>, Denise Jacobson<sup>2</sup>, Elizabeth Maleche-Obimbo<sup>3</sup>, Paige L. Williams<sup>2</sup>, Andrew Colin<sup>4</sup>, Meyer Kattan<sup>5</sup>, Sherry Eskander<sup>6</sup>, Michael H. Chung<sup>7</sup>, Kristina Crothers<sup>1</sup>, for the Pediatric HIV/AIDS Cohort Study (PHACS)

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of Nairobi, Nairobi, Kenya, <sup>4</sup>University of Miami, Miami, FL, USA, <sup>5</sup>Columbia University, New York, NY, USA, <sup>6</sup>Coptic Hope Center, Nairobi, Kenya, <sup>7</sup>Emory University, Atlanta, GA, USA

**Background:** Chronic lung disease (CLD) is an emerging comorbidity among youth living with perinatally-acquired HIV (YPHIV) globally. Obstructive CLD, particularly with irreversible airflow obstruction (AFO) such as with obliterative bronchiolitis and poorly controlled asthma, may be an important subtype. We hypothesized that AFO, with and without reversibility, is common in low/middle-income and high-income settings but that risk factors, including growth deficiencies, tobacco smoke exposure and immune imbalance (low CD4/CD8) differ across settings.

**Methods:** We performed a cross-sectional analysis of YPHIV (10–21 years old) in the Kenyan BREATHE (n=204) and US Pulmonary Complications in the Pediatric HIV/AIDS Cohort (PCPA; n=188) studies. Sociodemographic, clinical, immune function, and spirometry data were ascertained within 3 months of enrollment. AFO was defined as a z-score <-1.64 for the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (GLI 2012); irreversible AFO also required post-bronchodilator FEV1 increase ≤10%. We fit modified log-binomial models using generalized estimating equations with robust variances to estimate prevalence ratios (PR) of AFO by country. Wasting and stunted growth were defined as BMI- and height-for-age z-score <-2, respectively.

**Results:** Kenyan YPHIV were younger, had more wasting and stunting, and had lower CD4/CD8 (Table) despite 99% current antiretroviral therapy use in Kenyan compared to 89% in US YPHIV. Of Kenyan YPHIV, 24 (12%) had AFO and 13 (7%) had irreversible AFO compared to 26 (14%) and 16 (9%) US YPHIV, respectively. Among Kenyan YPHIV, stunted growth was associated with AFO (PR=2.60 [95%CI 1.25–5.41], p=0.01); wasting was associated with irreversible AFO (4.62 [1.39–15.42], p=0.01). Among US YPHIV, stunted growth was associated with irreversible AFO (3.27 [1.12–9.56], p=0.03); lower CD4/CD8 was associated with AFO (2.17 [0.99–4.76], p=0.05) and irreversible AFO (2.86 [0.93–9.09], p=0.07). We detected no associations with tobacco smoke exposure.

**Conclusion:** The prevalence of AFO and irreversible AFO was similar in Kenyan and US YPHIV. Deficits in growth parameters were associated with AFO, including irreversible AFO, in both Kenyan and US YPHIV. Immune imbalance was consistent with a greater likelihood of AFO among US YPHIV. Our findings suggest that these CLD manifestations are similar across settings despite differences in risk factor prevalence, highlighting an urgent need to elucidate common pathways in CLD among YPHIV.

|   | Kenyan YPHIV (n=204) | US YPHIV (n=188)    |
|---|----------------------|---------------------|
| Age at spirometry (years)                   | 14.6 (12.7, 18.3)    | 16.8 (14.2, 18.8)   |
| Female sex                                  | 92 (45%)             | 109 (58%)           |
| CD4 T-cell count (cells/μL)                 | 593 (389, 809)       | 635 (458, 783)      |
| CD4/CD8 ratio                               | 0.74 (0.38, 1.01)    | 0.91 (0.55, 1.25)   |
| Active tobacco smoking                      | 0 (0%)               | 16 (9%)             |
| Passive tobacco smoke exposure              | 47 (23%)             | 18 (10%)            |
| Wasting (BMI-for-age z-score <-2)           | 23 (11%)             | 8 (4%)              |
| Stunted growth (height-for-age z-score <-2) | 44 (22%)             | 20 (11%)            |
| FEV1 z-score, pre-bronchodilator            | -0.43 (-1.26, 0.38)  | -0.01 (-1.03, 0.70) |
| FEV1 z-score, post-bronchodilator           | -0.19 (-0.96, 0.54)  | 0.15 (-0.69, 1.07)  |
| FEV1/FVC z-score, pre-bronchodilator        | -0.11 (-0.99, 0.44)  | -0.39 (-1.01, 0.21) |

Data are presented as median (interquartile range) or n (%).

## 612 SERUM BIOMARKERS IDENTIFY CARDIAC DYSFUNCTION IN YOUTH LIVING WITH HIV

Andrew McCrary<sup>1</sup>, Winstone Nyandiko<sup>2</sup>, Michael J. Muehlbauer<sup>1</sup>, Ibrahim Daud<sup>3</sup>, Nathan M. Thielman<sup>1</sup>, Maggie Nguyen<sup>1</sup>, Svati J. Shah<sup>1</sup>, Gerald S. Bloomfield<sup>1</sup>

<sup>1</sup>Duke University, Durham, NC, USA, <sup>2</sup>Moi University, Eldoret, Kenya, <sup>3</sup>Walter Reed Project—Kericho, Kericho, Kenya

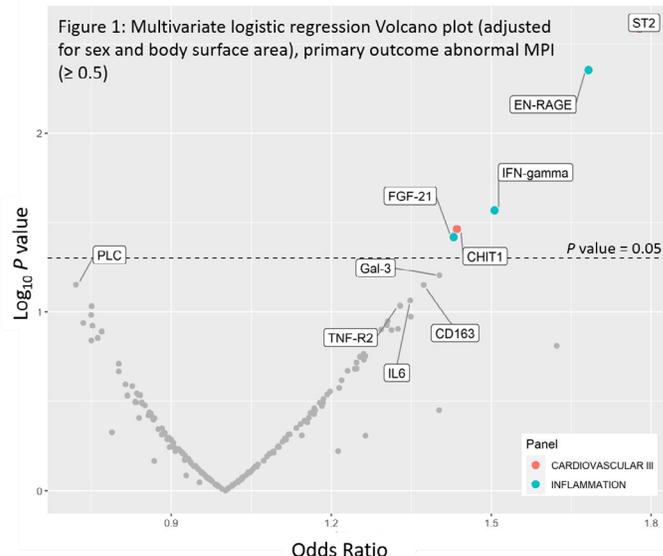
**Background:** In adults with HIV, fibrotic and inflammatory pathways are associated with cardiac dysfunction. It is not clear whether these associations are related to aging and lifestyle. We hypothesized that evaluating proteins in youth perinatally infected with HIV would help clarify this question, as well as identify biomarkers of cardiac dysfunction.

**Methods:** A total of 176 children and young adults perinatally infected with HIV selected from a previous study at Moi Teaching and Referral Hospital, Eldoret,

Kenya, of which 88 (50%) had abnormal tissue Doppler derived myocardial performance index (MPI - global measure of left ventricular systolic and diastolic function) and 88 had normal MPI. Using the Olink platform (PEA - antibody assays coupled with an oligonucleotide for specificity), we profiled 184 proteins in plasma samples. Univariate logistic regression was used to determine association between individual proteins with MPI status (False Discovery Rate adjusted for multiple comparisons) and multivariable models adjusted for sex and body surface area were constructed for significant proteins. A Lasso regression was also used to construct a model most discriminate of abnormal MPI.

**Results:** The median age of the study population was 14.3 years (IQR 8.1). In the univariate model, 18 proteins were significantly associated with MPI status after FDR adjustment. Of these, 5 remained significant in multivariable models: ST2 (adverse cardiac remodeling, OR 1.8 CI 1.2, 2.6), EN-RAGE (pro-inflammatory associated with coronary heart disease, OR 1.7 CI 1.2, 2.4), CHIT1 (inflammatory mediator associated with heart failure with preserved ejection fraction OR 1.4 CI 1.0, 2.0), and FGF-21 (metabolic homeostasis and insulin sensitivity, OR 1.5 CI 1.0, 2.0) (Figure 1). In an orthogonal approach, the Lasso regression also identified these four primary proteins as well as COL1A1, uPA, CST5, TIMP4, IL-6RA, IL-17A, CCL16, CTSD, and TNFRSF10C (AUC 0.818, CI 0.756, 0.880).

**Conclusion:** Using proteomics profiling in a unique cohort of children and young adults perinatally infected with HIV from Kenya, we identified proteins reporting on cardiac remodeling, inflammation and metabolism with higher circulating levels in young individuals with subclinical cardiac dysfunction. These results suggest that pathways dysregulated in overt adult HIV-related cardiovascular disease may also be dysregulated early in the HIV process and thus could serve as biomarkers for those at greatest risk of future cardiovascular disease.



## 613 ASSOCIATIONS OF GUT MARKERS WITH BODY FAT IN YOUTH WITH PERINATALLY ACQUIRED HIV

Sahera Dirajjal-Fargo<sup>1</sup>, Denise Jacobson<sup>2</sup>, Wendy Yu<sup>2</sup>, Ayesha Mirza<sup>3</sup>, Mitchell E. Geffner<sup>4</sup>, Jennifer Jao<sup>5</sup>, Grace A. McComsey<sup>6</sup>, for the Pediatric HIV/AIDS Cohort Study (PHACS)

<sup>1</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of Florida, Gainesville, FL, USA, <sup>4</sup>Kabwohe Clinical Research Center, Kabwohe, Uganda, <sup>5</sup>Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA, <sup>6</sup>University Hospitals Cleveland Medical Center, Cleveland, OH, USA

**Background:** Combination antiretroviral therapy (cART) has allowed youth with perinatal HIV infection (YPHIV) to survive into adulthood. Similar to adults, YPHIV experience unfavorable body composition changes of unclear mechanism. The role of gut dysfunction on body composition in YPHIV has not been investigated.

**Methods:** The PHACS Adolescent Master Protocol (AMP) study began enrolling YPHIV in 2007 across 15 U.S. sites, including Puerto Rico. We included YPHIV aged 7–19 yr with body composition data assessed by whole-body dual energy

x-ray absorptiometry (DXA) and HIV RNA  $\leq 1,000$  copies/mL within 3 mo of the first DXA (baseline). Among those with a DXA 2 yr later, we only included those with HIV RNA  $\leq 1,000$  copies/mL within 3 months of both DXA. Plasma levels of zonulin (a marker of intestinal permeability), intestinal fatty-acid binding protein (I-FABP, a marker of gut epithelial integrity), and lipopolysaccharide binding protein (LBP, a marker of microbial translocation) were measured by ELISA, within 6 mo of the first DXA. We assessed the association of baseline log<sub>10</sub> transformed gut markers with total body and trunk fat at baseline and at 2 yr using linear regression models adjusted for potential confounders (Black vs. non-Black, Tanner stage, and sex).

**Results:** 261 youth were included; 128 had a second DXA. Median age at the time of first DXA (Q1, Q3) was 12 yr (10, 14), 49% were female, and 67% were Black. Median CD4 cell count was 761 cells/mm<sup>3</sup>; 90% had HIV RNA < 400 copies/mL; 49% were on PI-, 16% on NNRTI-, 35% on other ART. Only 1 received INSTI-based ART. Baseline median (Q1,Q3) percent total body fat was 21.58% (14.94, 29.24) and trunk fat 41.28% (36.84, 45.96). The median percent increase in total body and trunk fat at 2 yr was 24.83% (8.70, 47.32) and 31.45% (12.16, 58.57), respectively. Distributions of I-FABP, LBP, and zonulin were not significantly different by cART or baseline CD4 cell count. In adjusted analyses, I-FABP was inversely related to percent total body fat at baseline and 2 yr, whereas LBP and zonulin were positively associated with total body fat at both time points (Table); no gut markers were associated with changes from baseline in total body or trunk fat.

**Conclusion:** Despite viral suppression, intestinal damage and the resultant bacterial translocation may influence body composition in YPHIV. Further studies are needed to investigate the role of gut dysfunction on body composition in YPHIV and elucidate underlying mechanisms.

Unadjusted and adjusted models assessing the association of each baseline gut marker with body fat outcomes

| Outcome                                 | Unadjusted |                       |         | Adjusted* |                       |         |
|---|------------|-----------------------|---------|-----------|-----------------------|---------|
|   | N          | E estimates (95% CI)  | P-value | N         | E estimates (95% CI)  | P-value |
| <b>Log<sub>10</sub> I-FABP (pg/mL)</b>  |            |                       |         |           |                       |         |
| Baseline % body fat                     | 261        | -3.06 (-4.95, -1.17)  | 0.002   | 241       | -2.22 (-4.07, -0.38)  | 0.018   |
| Baseline % trunk fat                    | 261        | -0.38 (-1.87, 1.10)   | 0.61    | 241       | -0.56 (-1.82, 0.69)   | 0.38    |
| Year 2 % body fat                       | 128        | -4.74 (-7.68, -1.80)  | 0.002   | 118       | -2.48 (-5.19, 0.23)   | 0.072   |
| Year 2 % trunk fat                      | 128        | -1.39 (-3.65, 0.88)   | 0.23    | 118       | -1.10 (-3.21, 1.02)   | 0.31    |
| % change in body fat                    | 128        | 0.46 (-8.47, 9.39)    | 0.92    | 118       | 0.36 (-8.84, 9.55)    | 0.94    |
| % change in trunk fat                   | 128        | -1.06 (-11.68, 9.55)  | 0.84    | 118       | -1.93 (-13.12, 9.27)  | 0.74    |
| <b>Log<sub>10</sub> LBP (ng/mL)</b>     |            |                       |         |           |                       |         |
| Baseline % body fat                     | 260        | 3.62 (0.99, 6.26)     | 0.007   | 240       | 4.19 (1.75, 6.64)     | <0.001  |
| Baseline % trunk fat                    | 260        | 1.42 (-0.21, 3.04)    | 0.087   | 240       | 0.43 (-1.07, 1.93)    | 0.57    |
| Year 2 % body fat                       | 128        | 3.60 (-0.30, 7.50)    | 0.071   | 118       | 3.83 (0.56, 7.10)     | 0.022   |
| Year 2 % trunk fat                      | 128        | 1.14 (-1.21, 3.49)    | 0.34    | 118       | -0.17 (-2.60, 2.25)   | 0.89    |
| % change in body fat                    | 128        | -1.09 (-13.19, 11.01) | 0.86    | 118       | -0.15 (-13.89, 13.39) | 0.98    |
| % change in trunk fat                   | 128        | -2.30 (-17.16, 12.56) | 0.76    | 118       | -1.41 (-18.43, 15.61) | 0.87    |
| <b>Log<sub>10</sub> zonulin (ng/mL)</b> |            |                       |         |           |                       |         |
| Baseline % body fat                     | 261        | 6.63 (5.95, 7.30)     | <0.001  | 241       | 6.45 (5.71, 7.20)     | <0.001  |
| Baseline % trunk fat                    | 261        | 1.28 (0.60, 1.97)     | <0.001  | 241       | 0.99 (0.27, 1.71)     | 0.007   |
| Year 2 % body fat                       | 128        | 7.05 (5.93, 8.18)     | <0.001  | 118       | 6.35 (5.15, 7.56)     | <0.001  |
| Year 2 % trunk fat                      | 128        | 1.05 (0.03, 2.06)     | 0.043   | 118       | 0.54 (-0.38, 1.46)    | 0.25    |
| % change in body fat                    | 128        | 0.66 (-4.17, 5.49)    | 0.79    | 118       | 0.88 (-5.82, 7.19)    | 0.84    |
| % change in trunk fat                   | 128        | 0.17 (-5.84, 5.98)    | 0.95    | 118       | 0.58 (-7.54, 8.70)    | 0.89    |

\*Models are adjusted for Tanner stage (2, 3, and 4-5 vs 1), race (Black vs non-Black), and sex.

I-FABP= intestinal fatty-acid binding protein, LBP= lipopolysaccharide binding protein

**614 GLOBAL TRENDS IN PEDIATRIC ON-TREATMENT MORTALITY ADJUSTED FOR LOSS TO CARE BIASES**

**Reshma Kassanjee<sup>1</sup>, Elizabeth Zaniewski<sup>2</sup>, Constantin Yiannoutsos<sup>3</sup>, Sophie Demonde<sup>4</sup>, Andrew Edmonds<sup>5</sup>, Tavitiya Sudjaritruk<sup>6</sup>, Jorge Pinto<sup>7</sup>, Désiré Lucien Dahourou<sup>8</sup>, Rachel C. Creeman<sup>9</sup>, Christelle Twizere<sup>10</sup>, Azar Kariminia<sup>11</sup>, James G. Carlucci<sup>12</sup>, Charles Kasozi<sup>13</sup>, Leigh Johnson<sup>1</sup>,** for the **leDEA International Epidemiology Databases to Evaluate AIDS (leDEA) Collaboration**

<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>University of Bern, Bern, Switzerland, <sup>3</sup>Indiana University Fairbanks School of Public Health, Indianapolis, Indiana, USA, <sup>4</sup>Inserm U1027/University Toulouse 3, Toulouse, France, <sup>5</sup>The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, <sup>6</sup>Chiang Mai University, Chiang Mai, Thailand, <sup>7</sup>School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil, <sup>8</sup>Centre Muraz, Bobo-Dioulasso, Burkina Faso, <sup>9</sup>Aaron Diamond AIDS Research Center, New York, NY, USA, <sup>10</sup>Centre National de Référence en matière de VIH/SIDA, Bujumbura, Burundi, <sup>11</sup>University of New South Wales, Sydney, Australia, <sup>12</sup>Vanderbilt University, Nashville, TN, USA, <sup>13</sup>Masaka Regional Referral Hospital, Masaka, Uganda

**Background:** UNAIDS projections of pediatric HIV prevalence and deaths rely on the International epidemiology Databases to Evaluate AIDS (leDEA) Consortium for mortality estimates among children with HIV (CHIV) receiving antiretroviral therapy (ART). Previous estimates may no longer be accurate due to expanded pediatric HIV care and treatment, and the possibility of unreported deaths in

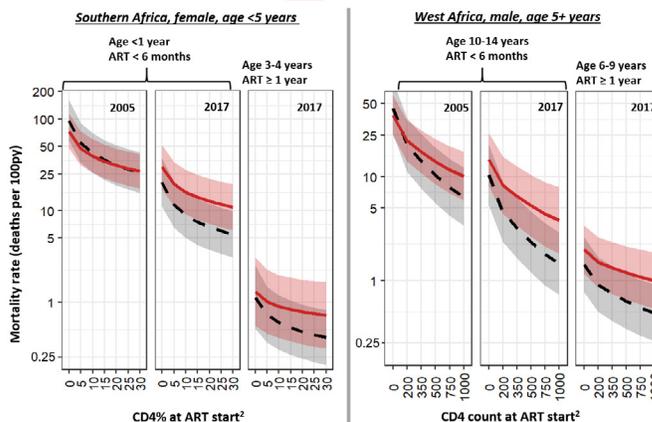
CHIV considered lost to follow-up (LTFU). We estimated all-cause mortality and its trends using both i) leDEA observational data from CHIV in routine care, and (ii) novel data from leDEA tracing studies that determined mortality outcomes in a sample of CHIV LTFU.

**Methods:** We included 47,279 CHIV (<15 years old) on ART within 2004-2017 at 72 sites in Africa, Asia, the Caribbean, and Central/South America. We used mixed-effect Poisson regression models to estimate mortality by age, sex, CD4 at ART start, time on ART, region, and calendar period (using linear splines). In an adjusted analysis, we modified the data before model-fitting by simulating mortality outcomes for a further 6 months in those identified as LTFU, based on a Gompertz survival model fitted to leDEA tracing study data (n=221), and combined results of multiple simulations using Rubin's rules.

**Results:** In the unadjusted analysis, 3217 deaths were recorded during 183,989 years of observation. Amongst African CHIV <5 years old, mortality was highest in the first 6 months of ART, lower at 0.5-1 year (rate ratio: 0.37; 95% CI: 0.31-0.34), and lowest at >1 year (0.15; 0.06-0.36) of ART. Compared to CHIV 3-4 years old, mortality was twice (2.24; 1.93-2.60) and 6-fold higher (5.67; 4.71-6.82) in 2-3 and <1-year-olds, respectively. Compared to CHIV with a CD4 <5% at ART start, mortality halved with CD4 5-10% (0.57; 0.52-0.63), with further reductions at higher CD4%. Results were similar for regions outside of Africa. In CHIV 5-14 years old, associations between mortality and ART duration or CD4 were similar. Fitted temporal trends indicate an average 68% reduction in mortality from 2005 to 2017 (33-90% by region and risk group). Adjusted mortality estimates were approximately double unadjusted ones in 2017 (Figure), with the average reduction from 2005 now 40%.

**Conclusion:** Mortality among CHIV has decreased over time, after controlling for lower mortality at longer ART durations, higher CD4 values and older ages. However, mortality estimates in recent years doubled when accounting for worse outcomes among those LTFU, reducing these apparent temporal improvements.

**Figure.** Estimated mortality rates (and 95% CIs) among CHIV on ART for a sample<sup>a</sup> of regions, risk groups, and years: **Unadjusted estimates** using observational data as is (—) and **adjusted estimates** after accounting for deaths in those otherwise considered LTFU (—).



<sup>a</sup>Sets of model covariate values were chosen to illustrate high and low mortality rate groups, temporal trends, patterns with CD4, and the impact of adjusting for deaths in LTFU – remaining results show similar patterns.  
<sup>2</sup>Intervals of CD4 values – axis labels indicate lower limits of intervals.

**615 MORTALITY IN CHILDREN & YOUTH (<25 YEARS) WHO STARTED ART BUT ARE LOST TO CARE**

**Patience Nyakato<sup>1</sup>, Morna Cornell<sup>2</sup>, Benedikt Christ<sup>3</sup>, Nanina Anderegg<sup>3</sup>, Josephine Muhairwe<sup>4</sup>, Laura Jefferys<sup>5</sup>, Janneke Van Dijk<sup>6</sup>, Monique Van Lettow<sup>7</sup>, Cleophas Chimbetete<sup>8</sup>, Sam J. Phiri<sup>9</sup>, Michael J. Vinikoor<sup>10</sup>, Matthias Egger<sup>3</sup>, Marie Balfanz<sup>1</sup>, Mary-Ann Davies<sup>1</sup>**

<sup>1</sup>Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa, <sup>2</sup>University of Cape Town, Cape Town, South Africa, <sup>3</sup>Institute of Social and Preventive Medicine, Bern, Switzerland, <sup>4</sup>SolidarMed, Maseru, Lesotho, <sup>5</sup>SolidarMed, Pemba, Mozambique, <sup>6</sup>SolidarMed, Masvingo, Zimbabwe, <sup>7</sup>Dignitas International, Zomba, Malawi, <sup>8</sup>Newlands Clinic, Harare, Zimbabwe, <sup>9</sup>Lighthouse Trust Clinic, Lilongwe, Malawi, <sup>10</sup>Center for Infectious Disease Research in Zambia, Lusaka, Zambia

**Background:** Despite significant progress in addressing HIV/AIDS, children, adolescents and young adults living with HIV (CAYHIV) continue to have poorer outcomes than adults aged  $\geq 25$  years. Loss to follow up (LTF) in antiretroviral therapy (ART) programs is a major challenge to achieving optimal treatment

outcomes and the UNAIDS 2030 target. We aimed to compare site-reported mortality with mortality among patients confirmed LTF who were traced.

**Methods:** We included routine observational data on patients initiating ART between 2004-2017 who were not traced, and data obtained from tracing studies for those who were traced from five countries (Lesotho, Malawi, Mozambique, Zambia and Zimbabwe) in Southern Africa. We used Mantel Haensel rates to estimate the crude survival function of mortality and rate ratios. We used random effects Weibull distribution models to examine factors associated with mortality among CAYHIV confirmed LTF and among routinely observed patients. We define LTF as having no recorded visit in the facility for  $\geq 182$  days and not known to be deceased or transferred out.

**Results:** We included 106,927 patients from the routine observational cohort and 680 patients who were selected through stratified random sampling and successfully traced (vital status ascertained). There were 2,506/106,927 (2.3%) deaths observed in the routine data and 62/680 (9.1%) additional deaths from tracing. The overall mortality rate in the first five years on ART was 1.25 (95% confidence interval (CI): 1.20, 1.30) per 100 person-years (py) among routine cohort patients and 6.70 (95% CI: 5.18, 8.67) per 100 py among traced patients. Higher mortality (Table 1) in the observational data was associated with being male, younger age at ART start, shorter duration on ART, and initiating ART after 2006. In the tracing data, younger age at ART start compared to 20-24 years and shorter duration on ART were associated with higher mortality.

**Conclusion:** We observed far higher mortality among CAYHIV who were lost and traced compared to mortality reported at the facility. Program-level mortality estimates among CAYHIV are likely to be underestimated if there is no additional outcome ascertainment done among those considered LTF.

## 616 MICROBIOLOGICAL FEATURES AND FOLLOW-UP OF NEONATES BORN TO MOTHERS WITH COVID-19

**Sara Vigil Vázquez**<sup>1</sup>, Itziar Carrasco<sup>1</sup>, Alba Pérez Pérez<sup>1</sup>, Alicia Hernanz-Lobo<sup>1</sup>, Ángela Manzanarez<sup>1</sup>, Elena Márquez<sup>2</sup>, Olga Sanz<sup>2</sup>, Beatriz Pérez-Seoane<sup>3</sup>, Álvaro Solaz<sup>2</sup>, María Concepción Ortiz Barquero<sup>6</sup>, Monica Riaza<sup>7</sup>, Marta Pareja<sup>8</sup>, Manuel Sánchez-Luna<sup>1</sup>, María Luisa Navarro<sup>1</sup>, for GESNEO-COVID

<sup>1</sup>Hospital General Universitario Gregorio Marañón, Madrid, Spain, <sup>2</sup>Hospital San Pedro de Alcántara, Cáceres, Spain, <sup>3</sup>Hospital Reina Sofía, Tudela, Navarra, Spain, <sup>4</sup>Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain, <sup>5</sup>Hospital Universitario La Fe, Valencia, Spain, <sup>6</sup>Hospital Universitario de Badajoz, Badajoz, Spain, <sup>7</sup>Hospital Universitario HM Montepríncipe, Madrid, Spain, <sup>8</sup>Complejo Hospitalario Universitario de Albacete, Albacete, Spain

**Background:** Literature evaluating the effect of SARS-CoV-2 infection in exposed newborns during pregnancy is still scarce. Although a 3% rate of perinatal transmission has been described, there is not enough evidence of viral transmission in biological samples through microbiological techniques. Our aim is to describe perinatal transmission in newborns exposed to SARS-CoV-2 during pregnancy and their follow up.

**Methods:** The study period is from March 15 to November 30, 2020. Exposed newborns of SARS-CoV-2 infected mothers (with microbiologically confirmed COVID-19 disease during pregnancy or delivery) were included at 13 hospitals in Spain. Demographic, clinical and microbiological data were collected. Biological samples including nasopharyngeal swab, blood, urine, and meconium from newborns and blood, placenta, and breast milk from mothers were collected for reverse transcription polymerase chain reaction (RT-PCR) analysis.

**Results:** 282 exposed to SARS-CoV-2 neonates were recruited; 130 cases during the first wave (March 15-July 31) and 152 during the second one (August 1- November 30). The prematurity birth-rate was 20% and 13% respectively. Overall, eleven newborns were positive for RT-PCR in nasopharyngeal swab, eight of them during the first 24-48 hours after birth. Three of them presented viral load in urine sample and another three in meconium sample. Only one RT-PCR was positive in maternal blood samples (1/115) and placenta (1/81). All newborns blood samples collected at delivery were negative for RT-PCR (0/70). There was no viral load either in breast milk samples (0/79). Placental immuno-histochemistry performed for SARS-CoV-2 showed no virus (0/16). Two newborn death were described none of them related to SARS-CoV-2. Those newborns exposed to SARS-CoV-2 were asymptomatic and with normal weight and psychomotor development at 6-months follow-up.

**Conclusion:** Intrauterine SARS-CoV-2 transmission seems unlikely, describing a 3.9% rate of neonatal infection after delivery. A high rate of prematurity is described, mostly during the first wave. SARS-CoV-2 can be detected by RT-PCR in urine and meconium of neonates with positive nasopharyngeal RT-PCR,

whereas it has not been detected in any newborn blood. The detection in maternal blood and placenta was anecdotal and it was not detected in breast milk samples. Except for the complications derived from prematurity, exposed newborns evolution was satisfactory.

617



## SAFETY AND EFFICACY OF REMDESIVIR IN A PEDIATRIC COVID-19 POPULATION

**Flor Munoz**<sup>1</sup>, William Muller<sup>2</sup>, Amina Ahmed<sup>3</sup>, David Kimberlin<sup>4</sup>, Ana Mendez-Echevarria<sup>5</sup>, Janet S. Chen<sup>6</sup>, Mari Nakamura<sup>7</sup>, William Pomputius<sup>8</sup>, Zongbo Shang<sup>9</sup>, Henry N. Hulter<sup>9</sup>, Catherine O'Connor<sup>9</sup>, Heather Maxwell<sup>9</sup>, Kathryn Kersey<sup>9</sup>, Diana Brainard<sup>9</sup>, Pablo Rojo<sup>10</sup>

<sup>1</sup>Baylor College of Medicine, Houston, TX, USA, <sup>2</sup>Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, <sup>3</sup>Levine Children's Hospital at Atrium Health, Charlotte, NC, USA, <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>5</sup>La Paz University Hospital, Madrid, Spain, <sup>6</sup>Drexel College of Medicine, Philadelphia, PA, USA, <sup>7</sup>Boston Children's Hospital, Boston, MA, USA, <sup>8</sup>Children's Minnesota Hospital, Minneapolis, MN, USA, <sup>9</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>10</sup>Hospital 12 de Octubre, Madrid, Spain

**Background:** COVID-19 is generally a mild disease in children and infants. However, a small proportion develop severe disease requiring intensive care and ventilatory support. Remdesivir (RDV), a direct-acting nucleotide pro-drug inhibitor of viral RNA-dependent RNA polymerases, has been shown to shorten time to recovery in adults with severe COVID-19. The aim of this study is to evaluate the safety and efficacy of RDV in pediatric patients.

**Methods:** CARAVAN (NCT04431453) is an ongoing open-label study of RDV in hospitalized pediatric patients with PCR-confirmed COVID-19. IV RDV is given for up to 10 days: 200mg on Day 1 followed by 100mg daily in Cohort 1 (12 to <18y, weight  $\geq 40$ kg) or 5mg/kg on Day 1 followed by 2.5mg/kg daily in Cohorts 2-4 (28 days to <18y, stratified by weight). Safety is assessed by adverse events (AEs) and laboratory tests. Efficacy assessments include change in oxygen requirements and clinical status on a 7-point ordinal scale through Day 10.

**Results:** Preliminary results for the first 27 patients are presented. Median (range) age and weight were: Cohort 1, 15 (12-17)y and 84 (47-192)kg; Cohort 2, 8 (4-16)y and 27 (25-39)kg; Cohort 3, 3 (2-5)y and 16 (12-18)kg; Cohort 4, 6 (2-11)m and 7 (3-10)kg. Overall, 52% were <12y, 56% were female, and 96% had  $\geq 1$  comorbid medical condition. Median number of RDV doses was 5; most RDV discontinuations were due to clinical improvement. At baseline, 67% required supplemental oxygen, including 22% on invasive ventilation; at Day 10, the values were 26% and 15%, respectively. In total, 70% showed clinical improvement on the 7-point ordinal scale at Day 10. Most (78%) had  $\geq 1$  AE, including 17% with study drug-related AEs; 7% discontinued study drug due to an AE. Serious AEs were reported for 33% of patients; no SAEs were study drug related. Two patients died within 30 days of completing treatment. Grade 3 or 4 lab abnormalities were reported in 52%; those reported in  $\geq 1$  patient were decreased hemoglobin (n=5), and hypoglycemia, glycosuria, and increased PTT (n=2 each). No safety trends related to RDV were apparent.

**Conclusion:** Among pediatric patients aged 2m to 17y treated with RDV for COVID-19, 70% had clinical improvement. The study is ongoing; enrolment of full term and preterm neonates is pending determination of the dose to be evaluated.

618



## SARS-CoV-2 VACCINES INDUCE DURABLE NEUTRALIZING ANTIBODIES IN INFANT RHESUS MACAQUES

**Carolina Garrido**<sup>1</sup>, Alan D. Curtis<sup>2</sup>, Hongmei Gao<sup>1</sup>, David Montefiori<sup>1</sup>, Mark Tomai<sup>3</sup>, Pamela A. Kozlowski<sup>4</sup>, Lisa C. Lindesmith<sup>2</sup>, Ralph Baric<sup>2</sup>, Barney S. Graham<sup>5</sup>, Kizzmekia Corbett<sup>5</sup>, Darin Edwards<sup>6</sup>, Andrea Carfi<sup>6</sup>, Koen K. Van Rompay<sup>7</sup>, Kristina De Paris<sup>2</sup>, Sallie Permar<sup>8</sup>

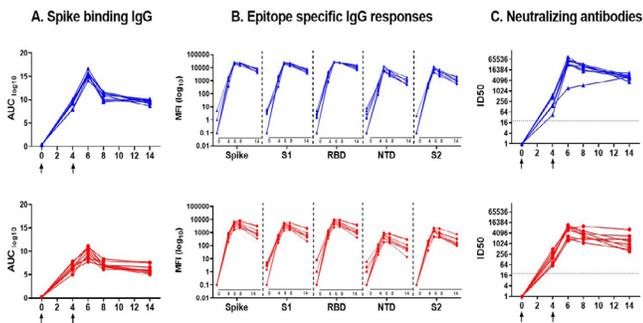
<sup>1</sup>Duke Human Vaccine Institute, Durham, NC, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>3M Corporate Research Materials Laboratory, Saint Paul, MN, USA, <sup>4</sup>Louisiana State University, New Orleans, LA, USA, <sup>5</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>6</sup>Moderna, Inc, Cambridge, MA, USA, <sup>7</sup>University of California Davis, Davis, CA, USA, <sup>8</sup>Weill Cornell Medicine, New York, NY, USA

**Background:** SARS-CoV-2 vaccines have shown promising efficacy in human adult trials, but immunogenicity and efficacy studies in the pediatric population are lagging behind. Here we evaluated the immunogenicity of two prefusion stabilized Spike protein (S-2P) vaccine platforms in infant Rhesus Macaques (RM): an adjuvanted S-P2 subunit and mRNA vaccine.

**Methods:** Infant RMs (2.5 months-old) were immunized intramuscularly at weeks (wks) 0 & 4 with 15 µg S-2P adjuvanted with the toll-like receptor 7/8 agonist 3M-052 in stable emulsion (n=8), or 30 µg of S-2P mRNA in lipid nanoparticles (mRNA-LNP, Moderna) (n=8). Blood was collected at wks 0, 4, 6, 8, & 14. Plasma (Spike[S]) and salivary (receptor binding domain [RBD]) IgG responses were measured by ELISA and epitope specificity by multiparameter bead array. Antibody function was assessed by an ACE2 blocking assay and neutralization by pseudovirus (PSVA) and whole virus neutralization assays, both with D614G. Flow cytometry was applied to measure S-specific memory B cells using fluorochrome-conjugated recombinant S, and S-specific IL-2, IL-17, TNF-α, or IFN-γ producing T cells after stimulation with overlapping peptides of full-length S.

**Results:** No adverse effects were observed with either vaccine. Plasma S-specific IgG responses were induced by both vaccines at wk 4, increased after the second dose, and persisted through wk 14 (Fig 1A). All S regions were targeted by plasma IgG (Fig 1B), and RBD-specific IgG was also detected in saliva. Serum antibodies achieved >95% ACE2 blocking by wk 6 (1:10 dilution), remaining >90% at wk 14. Geometric mean ID50 titers of neutralizing antibodies in the PSVA exceeded 10<sup>3</sup> from wk 6 through wk 14 (Fig 1C) and strongly correlated with whole virion neutralization (p<0.0001). In the protein vaccine group, S-specific CD27+ memory B cells peaked at 3.1% (mean) of total memory B cells; and S-specific CD4+ T cell responses were dominated by IL-17 and IFN-γ. Mean S-specific CD27+ B cells peaked at 0.9% total memory B cells in mRNA vaccinees and S-specific CD4+ T cells produced IL-2, IFN-γ, IL-17, or TNF-α.

**Conclusion:** The S-2P-3M-052-SE and mRNA-LNP vaccines were well-tolerated and highly immunogenic in infant Rhesus Macaques, with persistent IgG binding and neutralization responses that are comparable to those reported for adult RMs and humans. Our results provide proof-of-concept that a pediatric SARS-CoV-2 vaccine could induce long term protection against SARS-CoV-2.



**Figure 1:** S-specific plasma IgG responses in infant Rhesus Macaques after S-2P protein (blue triangles) or S-2P mRNA-LNP (red circles) vaccination. (A) AUC (log<sub>10</sub>) of S-specific IgG at wks 0, 4, 6, 8 and 14. (B) Epitope-specific responses expressed as log<sub>10</sub> MFI. (C) ID<sub>50</sub> (log<sub>10</sub>) values of neutralizing antibodies at wks 0, 4, 6, 8 and 14. Symbols and lines represent individual animals. Arrows indicate vaccinations.

**619 DIAGNOSTIC ACCURACY OF SARS-CoV-2 ANTIGEN RAPID TEST COMPARED TO REAL TIME PCR IN PED**

**Serena Villaverde**<sup>1</sup>, Sara Domínguez-Rodríguez<sup>1</sup>, Gema Sabrido<sup>2</sup>, MP Romero<sup>3</sup>, Marta Plata<sup>4</sup>, Ana Belén Jiménez<sup>5</sup>, Mar Nuñez<sup>6</sup>, Beatriz Soto<sup>7</sup>, David Molina-Arana<sup>8</sup>, Amanda Bermejo<sup>9</sup>, Manuel Gijón<sup>10</sup>, Begoña Pérez-Moneo<sup>11</sup>, Cinta Moraleda<sup>12</sup>, Alfredo Tagarro<sup>13</sup>, for the EPICO-AEP Working Group

<sup>1</sup>Instituto de Investigación Sanitaria Hospital 12 de Octubre (IMAS12), Madrid, Spain, <sup>2</sup>Pediatrics Department, Hospital Universitario Rey Juan Carlos, Móstoles, Spain, <sup>3</sup>Microbiology Department, Hospital Universitario La Paz, Madrid, Spain, <sup>4</sup>Pediatrics Emergency Department, Hospital Universitario La Paz, Madrid, Spain, <sup>5</sup>Pediatrics Department, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, <sup>6</sup>Pediatrics Emergency Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain, <sup>7</sup>Pediatrics Department, Hospital Universitario de Getafe, Getafe, Spain, <sup>8</sup>Microbiology Department, Hospital Universitario de Getafe, Getafe, Spain, <sup>9</sup>Pediatrics Department, Hospital Universitario de Móstoles, Móstoles, Spain, <sup>10</sup>Pediatrics Emergency Department, Hospital Universitario 12 de Octubre, Madrid, Spain, <sup>11</sup>Pediatrics Department, Hospital Universitario Infanta Leonor, Madrid, Spain, <sup>12</sup>Pediatric Infectious Diseases Unit, Department of Pediatrics, Hospital Universitario 12 de Octubre, Madrid, Spain, <sup>13</sup>Pediatrics Department, Hospital Universitario Infanta Sofía, San Sebastian de los Reyes, Spain

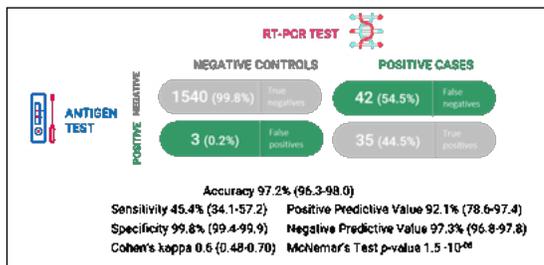
**Background:** The accuracy of rapid antigen tests (RAT) SARS-CoV-2 for in children is unknown. Our aim was to determine the diagnostic accuracy

and concordance of the RAT PanBio™ (Abbott) compared to RT-PCR in nasopharyngeal smear (NPS) samples, in symptomatic pediatric population.

**Methods:** This is a descriptive, retrospective, multicentre clinical study nested in a prospective, observational, multicenter cohort study. We included pediatric patients aged 0 to 16 years with symptoms consistent with COVID-19 of ≤5 days of evolution, attended in the Emergency Departments of the seven centers involved. A total of two consecutive NPS were obtained from each patient: one was employed to perform the RAT and the other to perform RT-PCR. Sample size for a non-inferiority study was calculated considering 80% power, for a 5% prevalence and a 90% sensitivity, using RT-PCR as the gold standard reference. A confusion matrix was displayed. Non-inferiority of sensitivity and specificity between diagnostic tests was assessed using the McNemar's test. The agreement between the two methods was calculated using Cohen's kappa index.

**Results:** A total of 1620 patients were tested in 7 hospitals. The overall sensitivity for RAT PanBio™ was 45.4% (95%CI, 34.1-57.2), and specificity was 99.8% (95%CI, 99.4-99.9) (Figure 1). The positive predictive value (PPV) for this 4.8% prevalence was 92.5% (95%CI, 78.6-97.4). The negative predictive value was 97.3 % (95%CI, 96.8-97.8). Positive likelihood ratio (PLR) was high - 233.8 (IC 95%, 73.5-743.3), and negative likelihood ratio (NLR) was low - 0.54 (95%CI, 0.44-0.67).

**Conclusion:** Compared to RT-PCR, the sensitivity of the RAT PanBio™ was low in children with <5 days of symptoms of COVID-19. The specificity and PLR were good, and the NLR and concordance with RT-PCR were only moderate. These results suggest that the test is very good when the result is positive, and that the test has only a limited value when the result is negative. In relation with screening and public health policy, these results should be interpreted considering also rapidness, availability and false positives ratio compared to RT-PCR or other tests.



**620 CLINICAL SYNDROMES CAUSED BY COVID-19 AND A BAYESIAN MODEL TO PREDICT SEVERITY**

**Alfredo Tagarro**<sup>1</sup>, Sara Domínguez-Rodríguez<sup>2</sup>, Serena Villaverde<sup>2</sup>, Miquel Serna-Pascual<sup>2</sup>, Francisco José Sanz-Santaufemia<sup>3</sup>, Carlos Grasa<sup>4</sup>, Antoni Soriano-Arandes<sup>5</sup>, Jesús Saavedra-Lozano<sup>6</sup>, Victoria Fumadó<sup>7</sup>, Cristina Epalza<sup>2</sup>, Jose Antonio Alonso<sup>3</sup>, Paula Rodríguez-Molino<sup>4</sup>, Joan Miquel Pujol<sup>5</sup>, Cinta Moraleda<sup>2</sup>, for the EPICO-AEP Working Group

<sup>1</sup>Hospital Universitario Infanta Sofía, Pediatrics Research Group., San Sebastian de los Reyes, Spain, <sup>2</sup>Hospital Universitario 12 de Octubre, Madrid, Spain, <sup>3</sup>Hospital Universitario Niño Jesús, Madrid, Spain, <sup>4</sup>Hospital Universitario La Paz, Madrid, Spain, <sup>5</sup>Hospital Universitario Vall d'Hebron, Barcelona, Spain, <sup>6</sup>Hospital Universitario Gregorio Marañón, Madrid, Spain, <sup>7</sup>Hospital Universitario Sant Joan de Deu Barcelona, Esplugues de Llobregat, Spain

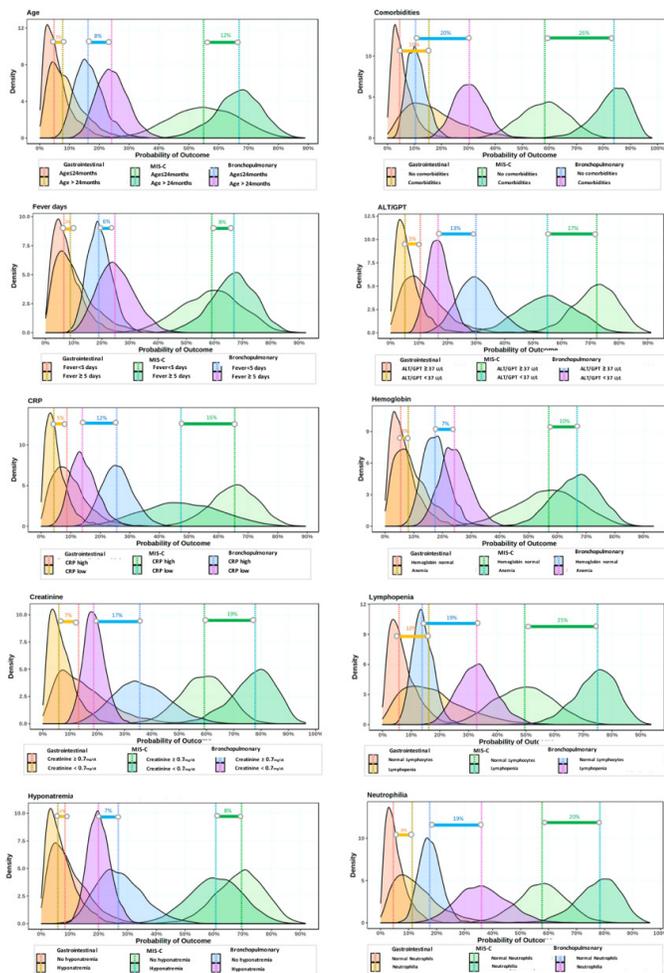
**Background:** This study aimed to identify the different syndromes presented in hospitalized children with SARS-CoV-2, to analyze if the clinical features and biomarkers confer different risk depending on the syndromes, and to create a predictive model to anticipate the probability of the need for critical care

**Methods:** We conducted a multicenter, prospective study of children aged 0 to 18 years old with SARS-CoV-2 infection in 52 Spanish hospitals. The primary outcome was the need for critical care: defined as the combined outcome of admission into a PICU, and/or need for respiratory support beyond nasal prongs. To understand the probability of needing critical care according to the diagnostic group and for each risk factor, a Bayesian multivariable model was applied. To build a predictive model of critical care, a naïve Bayes algorithm was implemented in a web app.

**Results:** 292 children were hospitalized from March 12th, 2020 to July 1st, 2020; Of them, 214 (73.3%) were considered to have relevant COVID-19 (r-COVID-19). Among patients with r-COVID-19, 24.2% needed critical care.

Out of 214 patients, 22.4% were admitted into a pediatric intensive care unit, 41.6% required respiratory support, and 38.8% presented complications (mostly cardiological). Four patients (1.8%) died, all of them had severe comorbidities. We identified 11 primary diagnoses and grouped them into 4 large syndromes of decreasing severity: MIS-C (17.3%), bronchopulmonary (51.4%), gastrointestinal (11.6%), and mild syndrome with complications (19.6%). In the predictive model, the predictors with higher relative importance were high C-reactive protein, anemia, lymphopenia, platelets <220 000/mm<sup>3</sup>, type of syndrome, high creatinine, and days of fever. The different risk factors increase the risk differently depending on the patient's syndrome: the more severe the syndrome, the more risk the factor confers. We developed an online risk prediction tool to quantify the risk of critical disease (<https://rserver.h12o.es/pediatrica/EPICOAPP/>, username: user, password:0000)

**Conclusion:** We described the spectrum of r-COVID-19 in hospitalized children, consisting of 4 large syndromes of decreasing severity: MIS-C, bronchopulmonary syndrome, gastrointestinal syndrome, and a mild syndrome with complications. The risk factors increase the risk differently depending on the syndrome. A Bayesian model was implemented in an online app to anticipate the individual risk of critical care.



**621 ELUCIDATING SARS-CoV-2 T-CELL RESPONSES IN PEDIATRIC COVID-19 AND MIS-C**

**Vidisha Singh<sup>1</sup>**, Veronica Obregon-Perko<sup>1</sup>, Stacey A. Lapp<sup>1</sup>, Anna M. Horner<sup>1</sup>, Alyssa Brooks<sup>1</sup>, Lisa S. McCoy<sup>1</sup>, Laila S. Hussaini<sup>1</sup>, Austin Lu<sup>1</sup>, Theda Gibson<sup>1</sup>, Evan Anderson<sup>1</sup>, Christina A. Rostad<sup>1</sup>, Ann Chahroudi<sup>1</sup>  
<sup>1</sup>Emory University, Atlanta, GA, USA

**Background:** Multisystem Inflammatory Syndrome in Children (MIS-C) can develop 1–2 mo post SARS-CoV-2 infection. MIS-C is characterized by fever, multiorgan dysfunction requiring hospitalization, and systemic inflammation. To evaluate a potential role for aberrant T-cell responses as a potential

mechanism for MIS-C pathogenesis, we quantified SARS-CoV-2-reactive T cells in children with COVID-19, MIS-C, and healthy children (HC).

**Methods:** Hospitalized children ages 0–20 yrs with COVID-19 (n=13) or MIS-C (n=18) were enrolled from May–Sep 2020. Peripheral blood mononuclear cells (PBMC) were obtained from convalescent phase of infection (28–54 d from illness onset) for COVID-19 or at hospitalization for MIS-C to approximate similar time since infection. Plasma SARS-CoV-2 receptor binding domain (RBD) antibody titers were determined by ELISA. PBMC from HC (n=20) with undetectable RBD antibodies served as controls. T-cell responses were quantified using activation-induced marker (AIM) assay after stimulation with SARS-CoV-2 peptide "megapools" (MP): CD4 MP\_S with 253 spike-spanning peptides, CD4 MP\_R with 221 remaining non-spike; spike-containing CD8 MP\_A and non-spike CD8 MP\_B with 314 each. Frequency of AIM+ T-cells and stimulation index (SI) were compared across donor groups.

**Results:** Among COVID-19, majority had SARS-CoV-2 specific CD4+ (100% spike, 83% non-spike) and CD8+ (85% spike-containing, 83% non-spike) T-cells. There was a trend for lower frequencies of AIM+ T-cells to all peptide MP in MIS-C, with significantly lower responses to non-spike antigens in CD4+ (p<0.05) and CD8+ (p<0.05) T-cells compared to those in COVID-19. In addition, COVID-19 had higher reactivity to stimulation, with significantly greater SI for spike CD4+ T-cell responses compared with HC (4.62 vs 1.93, p<0.05) and non-spike compared to both MIS-C (3.27 vs 1.44, p<0.05) and HC (3.27 vs 1.60, p<0.01). Interestingly, most HC also had detectable CD4+ (70% spike, 50% non-spike) and CD8+ T-cells (90% spike, 75% non-spike) against SARS-CoV-2 antigens, possibly attributable to prior infection by endemic coronaviruses. RBD IgG levels were similar between MIS-C and convalescent COVID-19.

**Conclusion:** We find more robust CD4+ and CD8+ T-cell responses against non-spike SARS-CoV-2 peptides in convalescent COVID-19 compared to MIS-C. Equivalent humoral responses against spike RBD among MIS-C and COVID-19 suggest that impaired SARS-CoV-2-specific T-cell response to non-spike antigens may contribute to the immunopathogenesis of MIS-C.

**622 ASYMPTOMATIC SARS-CoV-2 CHILDREN HAVE LOWER INFECTIVITY AND INTACT MEMORY RESPONSES**

**Nicola Cotugno<sup>1</sup>**, Alessandra Ruggiero<sup>1</sup>, Giuseppe R. Pascucci<sup>1</sup>, Bonfante Francesco<sup>2</sup>, Maria Raffaella Petrarà<sup>3</sup>, Bernardi Stefania<sup>1</sup>, Donato Amodio<sup>1</sup>, Piccioni Livia<sup>1</sup>, Daniele Donà<sup>3</sup>, Carlo Giaquinto<sup>3</sup>, Carlo Concato<sup>1</sup>, Petter Brodin<sup>4</sup>, Paolo Rossi<sup>1</sup>, Anita De Rossi<sup>3</sup>, Paolo Palma<sup>1</sup>

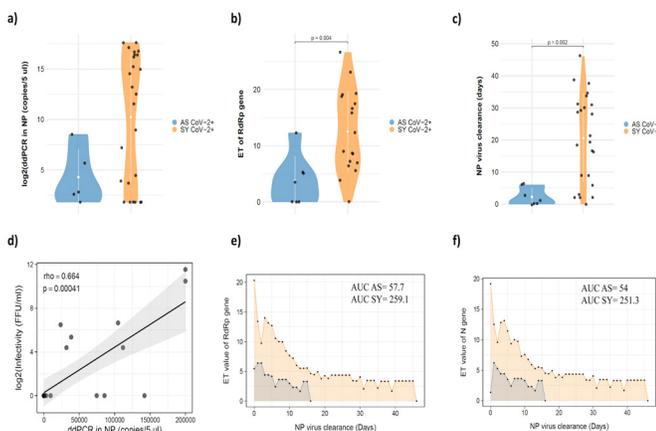
<sup>1</sup>Bambino Gesù Children's Hospital, Rome, Italy, <sup>2</sup>Istituto Zooprofilattico delle Venezie, Legnaro, Italy, <sup>3</sup>University of Padova, Padova, Italy, <sup>4</sup>Karolinska Institute, Stockholm, Sweden

**Background:** SARS-CoV-2 (CoV-2) infected children often range from being paucisymptomatic to fully asymptomatic. The impact of this population on the epidemics due to their ability to transmit the virus and achieve protective immunity has been poorly defined. We explored CoV-2 infectivity potential and anti-CoV-2 cellular (CD8, NK and B) and humoral response in symptomatic (SY) and asymptomatic (AS) CoV-2 infected children, screened for a family member resulted infected.

**Methods:** CoV-2 viral load was measured by RT-PCR and digital droplet PCR (ddPCR) on longitudinal samples of nasopharyngeal swabs in 9 AS and 33 SY (samples were paired according to symptoms onset for SY and first family contact for AS). Virus infectivity was tested by Virus focus forming assay (FFA). CoV-2 antibodies were investigated by Diasorin (CoV-2 Ab) and Ab-mediated neutralization activity (PRNT) at diagnosis, (samples collected >5 days from symptoms onset in SY, or from first family contact in AS were excluded from this timepoint), and in the convalescent phase (CP) (10–14 days after infection). Cellular response was analyzed by flow cytometry: 1) Ag-specific B cells, by a S1+S2 CoV-2-R-PE probe; 2) Ag-specific CD8+T cells by ICAM+; 3) natural-killer (NK) phenotype. Mann-Whitney was used for comparison; linear regression was used to evaluate the associations between virus load and infectivity.

**Results:** AS showed lower viral load (p=0.004) and faster virus clearance (p=0.0002) compared to SY. Virus infectivity was associated with ddPCR (rho=0.66; p=0.002). ASY and SY showed similar levels of CoV-2 Ab and PRNT, at both diagnosis and at follow up. During the CP, the proportion of CoV-2 Ab negative was 33,3% for both groups and PRNT was negative in 16,6% and 15,7% of AS and SY respectively. Anti-CoV-2 cellular immunity was comparable between ASY and SY. Indeed Ag-specific B cells and CD8 T cells were detectable despite symptomatology and no major differences were found between the

groups. Total NK frequency was similar between the groups, while a regulatory NK subset (CD56bright NK cells) was higher in AS compared to SY ( $p=0.01$ ). **Conclusion:** These data show that AS have a lower infectivity potential compared to SY suggesting that mitigated restrictive measures or alternative screening may be considered for this population. In addition, these patients showed an intact ability to produce humoral and cellular CoV-2 specific responses hence contributing to achieve herd immunity as much as SY.



**623 HIGH SPECIFIC IMMUNE RESPONSE AND LOW T-CELL ACTIVATION IN CHILDREN WITH COVID-19**

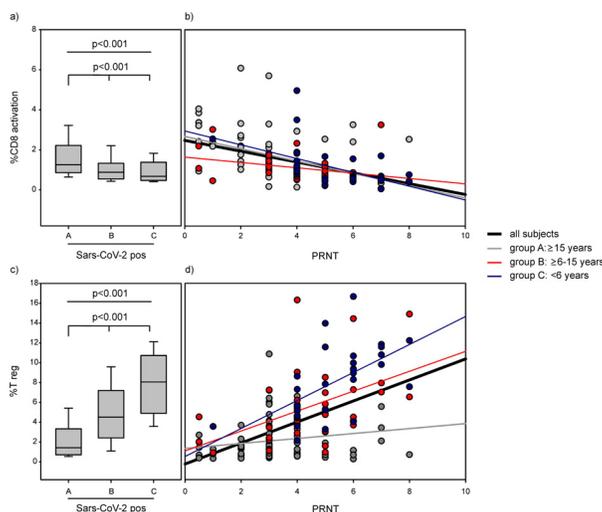
**Maria Raffaella Petrara**<sup>1</sup>, Bonfante Francesco<sup>2</sup>, Paola Costenaro<sup>1</sup>, Francesco Carmona<sup>3</sup>, Anna Cantarutti<sup>4</sup>, Elena Ruffoni<sup>3</sup>, Daniele Donà<sup>1</sup>, Costanza Di Chiara<sup>1</sup>, Marisa Zanchetta<sup>3</sup>, Luisa Barzon<sup>1</sup>, Carlo Giaquinto<sup>1</sup>, Anita De Rossi<sup>1</sup>  
<sup>1</sup>University of Padova, Padova, Italy, <sup>2</sup>Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro, Italy, <sup>3</sup>Veneto Institute of Oncology IOV, Padova, Italy, <sup>4</sup>University of Milano-Bicocca, Milan, Italy

**Background:** SARS-CoV-2 infected children are often asymptomatic or paucisymptomatic compared to adults. The immune response plays a pivotal role in dictating the clinical outcome in infected adults, but it is still poorly investigated in the pediatric population.

**Methods:** Fifty-seven family clusters of SARS-CoV-2, attending the Department for Women's and Children's Health (University of Padova), were enrolled between March and September 2020, for a total 209 subjects. SARS-CoV-2 infection was confirmed in 155 patients (SARS+: 93 ≥15 years [group A]; 34 children ≥6-15 years [group B]; 28 children <6 years [group C]) by virus molecular detection and/or serology. In 41 available samples, measurement of SARS-CoV-2 levels (VL) was performed by an in-house quantitative One-Step ddPCR method. A blood sample was obtained at a median [IQR] of 2.8 [2.1-3.7] months after baseline (symptom's onset and/or first positive virus detection). Neutralizing antibodies (Nabs) were detected by a Plaque Reduction Neutralization Test (PRNT). Activated (CD8+CD38+HLA-DR+) and regulatory T cells (T-reg; CD4+Foxp3+CD127-CD25+) were analyzed by flow cytometry.

**Results:** VL did not differ by age (18507 [326-339315], 6723 [3427-114587], and 21106 [162-152500] copies/5µl, in group A, B and C, respectively; overall,  $p=0.955$ ). Group C had the highest PRNT titer compared to the other groups (overall,  $p<0.0001$ ). Activated CD8 and regulatory T cells were significantly higher in SARS+ than in SARS- subjects ( $p<0.001$ ). CD8 activated cells were significantly higher in group A compared to the other groups ( $p<0.001$ ; Figure a), and were inversely correlated with PRNT titer (group A:  $rs=-0.527$ ,  $p<0.0001$ ; B:  $rs=-0.494$   $p=0.003$ ; C:  $rs=-0.547$   $p<0.0001$ ; Figure b). Conversely, T-reg were significantly higher in group C compared to the others ( $p<0.001$ ; Figure c), and were positively correlated with PRNT values in children (group C:  $rs=0.662$   $p=0.0001$ , B:  $rs=0.532$   $p=0.001$ ; A:  $rs=0.160$ ,  $p=0.125$ ; Figure d).

**Conclusion:** Levels of SARS-CoV-2 did not differ among age classes, but adults displayed a higher T cell activation and a lower production of anti-SARS Nabs than children. Conversely, younger infected children had the highest production of anti-SARS Nabs and the lowest non-specific T cell activation, most likely due to their higher expression of regulatory T cells.



**624 HIGH AND PERSISTENT NEUTRALIZING ANTIBODIES IN CHILDREN RECOVERED FROM COVID-19**

**Bonfante Francesco**<sup>1</sup>, Paola Costenaro<sup>2</sup>, Anna Cantarutti<sup>3</sup>, Costanza Di Chiara<sup>2</sup>, Chiara Cosma<sup>2</sup>, Alessio Bortolami<sup>1</sup>, Maria Raffaella Petrara<sup>2</sup>, Matteo Pagliari<sup>1</sup>, Sandra Cozzani<sup>2</sup>, Giovanni Di Salvo<sup>2</sup>, Liviana Da Dalt<sup>2</sup>, Luisa Barzon<sup>2</sup>, Anita De Rossi<sup>2</sup>, Daniele Donà<sup>2</sup>, Carlo Giaquinto<sup>2</sup>  
<sup>1</sup>Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro, Italy, <sup>2</sup>University of Padova, Padova, Italy, <sup>3</sup>University of Milano-Bicocca, Milano, Italy

**Background:** Recent evidences suggest that SARS-CoV-2 neutralizing antibodies (Nabs) may persist over time, however lack of knowledge still regards the pediatric population.

**Methods:** A single-centre, prospective observational study evaluated family clusters of COVID-19 attending the Pediatric Department, University Hospital of Padua (Italy). Confirmed COVID-19 was defined by positive SARS-CoV-2 molecular detection and/or serology; patients/family symptom's and virological positivity were considered to define the infection onset (baseline). Blood samples were analyzed in pair to detect Nabs through Plaque Reduction Neutralization Test (PRNT), and IgG through chemiluminescent immuno-enzymatic assay (CLIA) MAGLUMI™ 2000 Plus; IgG >1.1 kAU/L and/or PRNT ≥1:10 were considered positive. SARS-CoV-2 viral load (VL) was quantified by multiplex quantitative assay based on One-Step RT-ddPCR. Geometric mean titers (GMT) and 95% Confidence Intervals of IgG/PRNT were evaluated, stratified by age and time from baseline to sample collection. Trends over time of immune-virological response were assessed. P-value <0.05 was considered statistically significant.

**Results:** Among 213 subjects (57 families) evaluated, 155 had confirmed COVID-19 including 73 (47%) children/older siblings of 8 years median age (IQR 4-13) and 82 (53%) parents aged 42 years (IQR 34-46); 93.5% had asymptomatic/mild COVID-19. From the cumulative analysis of 194 blood samples, Nabs persisted over a median period of 95 days (IQR, 67-133) from baseline. Children showed significantly higher NAbs than older subjects, with children <3 years ranging from a 4-fold difference at 1-2 months to 8.8-fold difference at 3-6 months after baseline, compared to adults (table). The longitudinal assessment of 42 subjects sampled at 60 days (SD +/-9.9) and at 150 days (SD +/-24.2) showed a 2-fold increase in NAbs in children <6 years (PRNT 144, 95% C.I. 74.42-277.94 versus 303, 95% C.I. 196.43-468.57) and a substantial stability in Nabs among older subjects. CLIA IgG significantly decreased over time for all age classes, becoming negative in 13/42 subjects (31%), compared to 1/42 subjects detected by PRNT. Among 32 individuals checked for VL within 4 days from baseline, VL directly correlated with PRNT titers in subjects >15 years (Pearson Coefficient =0.70,  $p=0.0349$ ) but not in pediatric cases.

**Conclusion:** Asymptomatic/mild COVID-19 disease triggers in children a superior and persistent humoral response compared to adults.

| All data, irrespective of onset |                       |                     |                     |                    |          |
|---------------------------------|-----------------------|---------------------|---------------------|--------------------|----------|
| Age Classes (years)             | < 3 (n=22)            | 3 - 6 (n=18)        | 6 - 15 (n=38)       | ≥ 15 (n=116)       | p-value† |
|                                 | GMT (95% CI)          | GMT (95% CI)        | GMT (95% CI)        | GMT (95% CI)       |          |
| IgM (KAU/L) ‡                   | 0.69 (0.54 - 0.87)    | 0.79 (0.54 - 1.17)  | 0.5 (0.39 - 0.65)   | 0.52 (0.45 - 0.61) | 0.1016   |
| IgG (KAU/L) ‡                   | 2.71 (1.62 - 4.54)    | 2.78 (1.56 - 4.94)  | 2.54 (1.69 - 3.82)  | 1.31 (0.93 - 1.84) | 0.0382   |
| PRNT (endpoint titer)           | 320 (233.64 - 438.29) | 154 (87.9 - 269.65) | 98 (62.99 - 152.89) | 53 (42.83 - 64.58) | <0.0001  |

| At 1 - 2 months, from onset |                      |                     |                      |                    |          |
|-----------------------------|----------------------|---------------------|----------------------|--------------------|----------|
| Age Classes (years)         | < 3 (n=14)           | 3 - 6 (n=8)         | 6 - 15 (n=14)        | ≥ 15 (n=55)        | p-value† |
|                             | GMT (95% CI)         | GMT (95% CI)        | GMT (95% CI)         | GMT (95% CI)       |          |
| IgM (KAU/L) ‡               | 0.7 (0.57 - 0.87)    | 0.76 (0.48 - 1.22)  | 0.62 (0.5 - 0.78)    | 0.58 (0.48 - 0.7)  | 0.5518   |
| IgG (KAU/L) ‡               | 3.8 (1.96 - 7.34)    | 4.86 (2.4 - 9.85)   | 3.87 (1.85 - 8.09)   | 1.59 (0.94 - 2.72) | 0.0912   |
| PRNT (endpoint titer)       | 276 (171.44 - 443.8) | 95 (38.06 - 237.83) | 152 (83.82 - 276.63) | 59 (44.11 - 79.84) | <0.0001  |

| At 3 - 6 months, from onset |                       |                       |                     |                    |          |
|-----------------------------|-----------------------|-----------------------|---------------------|--------------------|----------|
| Age Classes (years)         | < 3 (n=8)             | 3 - 6 (n=10)          | 6 - 15 (n=24)       | ≥ 15 (n=61)        | p-value† |
|                             | GMT (95% CI)          | GMT (95% CI)          | GMT (95% CI)        | GMT (95% CI)       |          |
| IgM (KAU/L) ‡               | 0.66 (0.3 - 1.45)     | 0.83 (0.39 - 1.74)    | 0.44 (0.29 - 0.65)  | 0.48 (0.37 - 0.61) | 0.2855   |
| IgG (KAU/L) ‡               | 1.3 (0.71 - 2.38)     | 1.59 (0.67 - 3.78)    | 1.96 (1.2 - 3.22)   | 1.08 (0.69 - 1.68) | 0.4081   |
| PRNT (endpoint titer)       | 415 (307.46 - 560.13) | 226 (107.06 - 478.23) | 76 (40.97 - 140.79) | 47 (35.31 - 63)    | <0.0001  |

## 625 ROBUST HUMORAL IMMUNE RESPONSES TO SARS-CoV-2 INFECTION IN CHILDREN

**Carolina Garrido**<sup>1</sup>, Cynthia G. Lorang<sup>1</sup>, Jhoanna Z. Aquino<sup>2</sup>, M. Anthony Moody<sup>1</sup>, Sallie R. Permar<sup>1</sup>, Jillian H. Hurst<sup>3</sup>, Matthew S. Kelly<sup>2</sup>, Genevieve Fouda<sup>1</sup>  
<sup>1</sup>Duke Human Vaccine Institute, Durham, NC, USA, <sup>2</sup>Division of Pediatric Infectious Diseases, Duke University, Durham, NC, USA, <sup>3</sup>Division of Pediatric Infectious Diseases, Duke University, Durham, NC, USA

**Background:** The low susceptibility of children to severe illness with SARS-CoV-2 infection could be related to distinct virus-host interactions. Some studies indicate that SARS-CoV-2 infected adults with mild symptoms rapidly lose their antibody responses, but the kinetics of the antibody response in children have been less studied. To evaluate the antibody response of SARS-CoV-2 antibodies in infected children, we used samples from the Biospecimens from Respiratory Virus-Exposed Kids (BRAVE Kids) Study, a community-based prospective cohort study of children and adolescents with SARS-CoV-2 infection or exposure.

**Methods:** Samples from 71 SARS-CoV-2 infected children (median age: 9.7 years, IQR 4-16) collected at enrollment (M0), 2 and 4 months after exposure (M2, M4) were analyzed. A Luminex-based multiplex binding assay was used to measure Ig isotype (IgG, IgM, IgA) and IgG subclass (IgG1, IgG3) against 7 SARS-CoV-2 epitopes: whole spike (S), subunit 1 (S1), S2, receptor binding domain (RBD), N-terminal domain (NTD), nucleocapsid (NC) and membrane (M). The ability of antibodies to block viral interaction with the human receptor ACE2 was evaluated by an ELISA-based assay, and neutralization was assessed in a pseudovirus assay.

**Results:** At time of enrollment (median of 5 days after infection), all participants had detectable levels of IgM and IgA against at least one of the tested SARS-CoV-2 antigens, and 91% had detectable IgG levels. IgM and IgA levels declined with time, although all children still had detectable levels of anti-S IgM and IgA at M4. In contrast, IgG binding to all viral regions increased significantly at M2 and, at M4, most children maintained robust IgG response. IgG1 and IgG3 antibodies were detected against most antigens. ACE2 blocking increased at M2 as compared to M0, and at M2 the percent blocking was higher in younger children than in older children (Fig 1). Similarly, younger children had higher levels of anti-RBD IgG at M2, whereas older children showed higher levels of anti-RBD IgM. We found no differences in antibody profiles between asymptomatic and symptomatic children. Preliminary analysis in 4 children indicated that neutralizing antibody responses were still detectable at M4.

**Conclusion:** SARS-CoV-2 infected children develop robust antibody responses that are still detectable 4 months after infection. This suggests that children could respond well to SARS-CoV-2 vaccination and highlights the need to test candidate vaccines in pediatric populations.

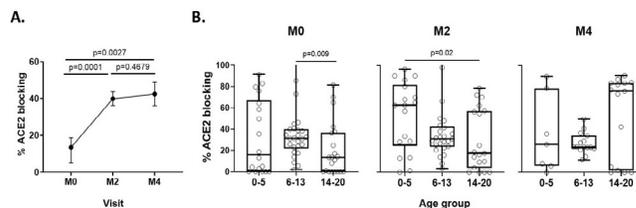


Figure 1. Antibody ACE2 blocking activity at time of exposure (M0), 2 months (M2) and 4 months (M4) after. A. Evolution of ACE2 blocking over time. Median with 95% CI. Wilcoxon matched-pairs signed rank test; B. ACE2 blocking activity divided by age group. Min to max. Mann Whitney test.

## 626 SARS-CoV-2 TESTING & POSITIVITY AMONG PERSONS WITH & WITHOUT HIV IN 6 US COHORTS

**Lesley S. Park**<sup>1</sup>, Kathleen A. McGinnis<sup>2</sup>, Kirsha Gordon<sup>2</sup>, Michael A. Horberg<sup>3</sup>, Celeena R. Jefferson<sup>4</sup>, Lisa Bastarache<sup>5</sup>, Srushti Gangireddy<sup>6</sup>, Michael J. Silverberg<sup>7</sup>, Wendy Leyden<sup>8</sup>, Sonia Napravnik<sup>9</sup>, Deana Agil<sup>9</sup>, Alison G. Abraham<sup>10</sup>, Gypsyamber D'Souza<sup>11</sup>, Kerri N. Althoff<sup>11</sup>, for the CIVET Collaboration of the NA-ACCORD of IeDEA  
<sup>1</sup>Stanford University, Stanford, CA, USA, <sup>2</sup>VA Connecticut Healthcare System, West Haven, CT, USA, <sup>3</sup>Kaiser Permanente Mid-Atlantic States, Washington, DC, USA, <sup>4</sup>Mid-Atlantic Permanente Research Institute, Rockville, MD, USA, <sup>5</sup>Aaron Diamond AIDS Research Center, New York, NY, USA, <sup>6</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>7</sup>Kaiser Permanente Division of Research, Oakland, CA, USA, <sup>8</sup>Kaiser Permanente, Oakland, CA, USA, <sup>9</sup>University of North Carolina, Chapel Hill, Chapel Hill, NC, USA, <sup>10</sup>University of Colorado Denver, Aurora, CO, USA, <sup>11</sup>Johns Hopkins University, Baltimore, MD, USA

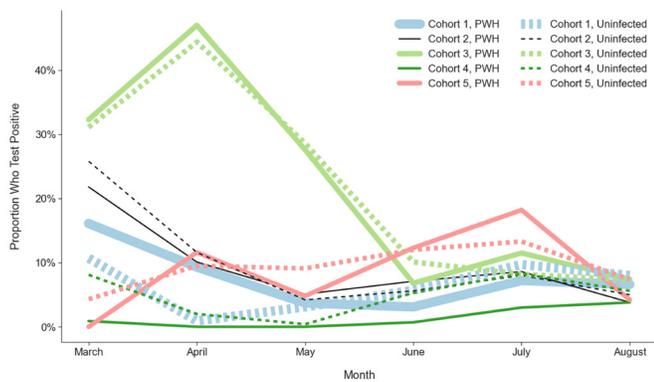
**Background:** It is not known if people with HIV (PWH) in the United States (US) have different access to SARS-CoV-2 RT-PCR (COVID-19) testing, or positivity proportions (among those tested), than people without HIV (PWOH). We describe COVID-19 testing and positivity proportions in 6 large geographically and demographically diverse cohorts of PWH and PWOH.

**Methods:** The Corona-Infectious-Virus Epidemiology Team (CIVET) is comprised of five COVID-19 clinical cohorts within a health system (Kaiser Permanente Northern California, Oakland, CA; Kaiser Permanente Mid-Atlantic States, Rockville, MD; University of North Carolina Health, Chapel Hill, NC; Vanderbilt University Medical Center, Nashville, TN; Veterans Aging Cohort Study) and one established classical HIV cohort (MACS/WIHS Combined Cohort Study). Each participating cohort is restricted to individuals who were alive and "in-cohort" in 2020 (definitions of which were operationalized to fit the structure of each cohort). We calculated the percentage of patients in-cohort who were COVID-19 tested, and the proportion COVID-19 positive monthly, by HIV status, from March 1 to August 31, 2020. We report findings from the classical cohort separately because results are based on self-reported information.

**Results:** In the 5 clinical cohorts, PWH ranged from N=2,515 to 31,040, and N=77,019 to 3,710,360 PWOH. Over the 6 month study period, the percentage of PWH who were tested for COVID-19 (13.5%-21.2%) was slightly higher than PWOH (10.8%-14.3%) in each of the cohorts (p-values in each cohort <0.001). However, among those tested, the percentage of patients with positive COVID-19 tests was similar regardless of HIV status (Figure). In the classical cohort that contributed self-reported testing and positive information (PWH N=2,222; PWOH N=1,417), the proportion tested was similar by HIV status (PWH 38.1% vs. PWOH 37.4%), but PWH had a greater positivity proportion (9.0%) compared with PWOH (5.3%, p-value=0.012).

**Conclusion:** Although PWH had higher testing rates compared with PWOH, we did not find evidence of increased positivity among those tested in 5 clinical cohorts with large diverse populations across the US. We will continue to monitor testing, positivity, and COVID-19 related health outcomes in PWH and PWOH using our multiple data sources and leveraging the expertise of established longitudinal cohort studies in the CIVETS collaboration.

**Figure:** The proportion SARS-CoV-2 RT-PCR detected test results in 5 clinical cohorts in the United States, by HIV status, March 1 - August 31, 2020



P-values comparing the positivity proportions by HIV status: cohort 1  $p=0.002$ ; cohort 2  $p=0.507$ ; cohort 3  $p=0.062$ ; cohort 4  $p<0.001$ ; cohort 5  $p=0.355$

**627 SARS-CoV-2 SEROPREVALENCE AND IgG LEVELS ARE LOWER AMONG PEOPLE LIVING WITH HIV**

**Matthew Spinelli**<sup>1</sup>, Kara A. Lynch<sup>1</sup>, Cassandra A. Yun<sup>1</sup>, Dave Glidden<sup>1</sup>, Michael A. Peluso<sup>1</sup>, Timothy A. Heinrich<sup>1</sup>, Monica Gandhi<sup>1</sup>, Lillian B. Brown<sup>1</sup>  
<sup>1</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** Although data are mixed, most cohorts show a similar or lower COVID-19 incidence among people living with HIV (PLWH) compared to the general population. However, incidence may be impacted by lower testing rates among vulnerable populations. We compared SARS-CoV-2 seroprevalence and IgG levels, and disease severity, among patients with and without HIV receiving care within a county hospital system over a three-month period.

**Methods:** From August through October 2020, remnant serum samples were collected from all PLWH who underwent routine outpatient laboratory testing at San Francisco General Hospital which houses a large HIV clinic (Ward 86). Patients with HIV were matched on time of collection (same day) and age (+/- 5 years) to 1-2 adults without HIV. SARS-CoV-2 levels of IgG levels was quantified in serum using the Pylon IgG assay (100% specificity on internal validation). Seroprevalence was compared by HIV status via conditional logit models, adjusting for sex. For those with reactive results, IgG levels were compared by HIV status using log-transformed generalized estimating equations. Severe disease, assessed via chart review, was defined as requiring oxygen.

**Results:** Among 1,411 individuals (46% PLWH), the median age was 58 (IQR: 49-65), 64% were men. COVID-19 seroprevalence was 3.1% among PLWH compared to 6.8% among people without HIV (adjusted odds ratio 0.41; 95% confidence interval (CI): 0.25-0.68,  $p<0.001$ ). Among those with reactive COVID-19 IgG results ( $n=72$ , 20 in PLWH); antibody levels were 47% lower among PLWH (95% CI: 19-65% lower;  $p=0.003$ ; Figure); however, there was a trend towards higher disease severity among PLWH [15% ( $n=3$ ) vs. 4% ( $n=2$ );  $p=0.13$ ].

**Conclusion:** Both seroprevalence, and absolute SARS-CoV-2 IgG levels in those with reactive results, were lower among PLWH, within a time and age-matched population of outpatients receiving routine laboratory testing in an urban hospital. PLWH may have had higher adherence to non-pharmaceutical interventions (NPIs) than those without HIV, leading to lower COVID-19 seroprevalence and, possibly, lower COVID-19 IgG levels if infected with a lower viral inoculum due to NPIs. Alternatively, PLWH may mount lower antibody responses to SARS-CoV-2, as has been demonstrated with hepatitis B and yellow fever vaccines. Further studies of COVID-19 susceptibility and immunity are needed among PLWH. Moreover, PLWH should be enrolled in SARS-CoV-2 vaccine studies or followed after vaccination to ensure they mount sufficient humoral responses.

**628 A POPULATION-BASED ANALYSIS OF SARS-CoV-2 AMONG PATIENTS ON ART OR PrEP**

**Kate Salters**<sup>1</sup>, Kiana Yazdani<sup>1</sup>, Paul Sereda<sup>1</sup>, David Moore<sup>1</sup>, Junine Toy<sup>1</sup>, Rolando Barrios<sup>1</sup>, Julio S. Montaner<sup>1</sup>

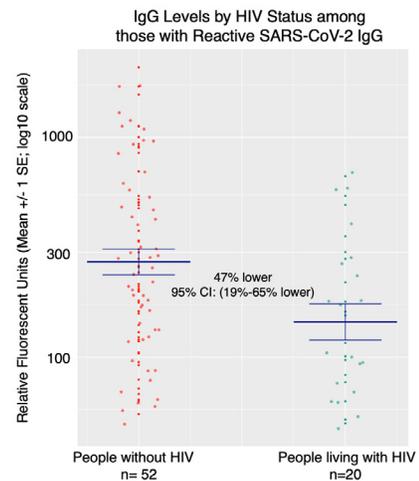
<sup>1</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada

**Background:** The novel SARS-CoV-2 pandemic first appeared in Canada in January 2020. Since November 22 2020, nearly 29,000 people in the province of British Columbia (BC) have been infected. New diagnoses have hit all-time daily highs in November, yet understanding the impact on those at risk of or living with HIV remains limited. Utilizing a population-based registry, we conducted an observational analysis of SARS-CoV-2 testing, positive cases, and outcomes among individuals receiving either HIV pre-exposure prophylaxis (PrEP) or antiretroviral therapy (ART) in BC.

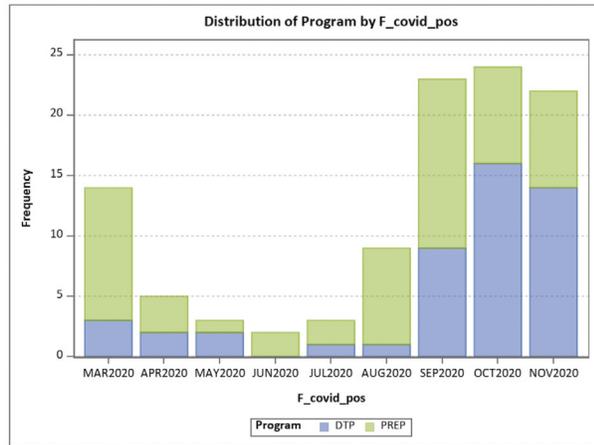
**Methods:** In BC, ART and PrEP are provided at no cost to medically eligible patients through the BC Centre for Excellence in HIV/AIDS Drug Treatment Program (DTP). The DTP registry includes adults aged 18 years and older who have been prescribed publicly funded ART since 1992 or PrEP since 2018. Since the start of 2020, data from the laboratory program and DTP registry has included daily counts for SARS-CoV-2 tests performed, antibody (Ab) and RNA test results, and mortality outcomes. In this analysis, we examine demographic characteristics of DTP patients who underwent testing and COVID-19 positive cases of from March 1 to November 22 2020.

**Results:** There were 48 (3.5%) patients diagnosed with COVID-19 among a cohort of 1,348 patients living with HIV on ART who were tested for the virus. In the PrEP cohort, there were 59 (4.5%) patients who were diagnosed with COVID-19 among the 1,304 PrEP patients tested for the virus at least once for COVID-19. There was no statistically significant ( $p=0.20$ ) difference between the proportion of positive cases in ART vs PrEP group (chi-squared test). Of the 107 DTP patients who tested positive for COVID-19, the median age was 40 years (51.5 for DTP patients; 32 years for PrEP patients), 97 (90.7%) were male, and 83 (77.6%) resided in the largely urban Vancouver Coastal Health Authority region. Importantly, COVID-19 positive cases among patients on ART (vs PrEP) and female patients (vs male) were more likely to be diagnosed in the second wave of the pandemic in BC (from September 2020 onwards). Promisingly, no deaths were reported among the sample as of November 22, 2020.

**Conclusion:** We observed similar proportions of COVID-19 positive tests among PrEP and ART patients tested in our provincial registry. Growing numbers of COVID-19 positive cases among patients in ART group during the pandemic's second wave is of significant concern for ongoing community transmission outbreaks.



**Table 1: New cases of COVID-19 among patients in DTP (people living with HIV) and patients on PrEP from March to November 2020**



**Table 1. Results of Exposure Questionnaires Performed on 187 People Living with HIV in Our Ryan White Clinic**

|  | Patients COVID-19 IgG negative (N=162) | Patients Covid-19 IgG positive (N=25) |
|--|--|---------------------------------------|
| Mean Age (Age, IQR)                      | 43 (34-56)                             | 53 (47-58)                            |
| Sex (N):                                 |  |                                       |
| Female                                   | 33                                     | 1                                     |
| Male                                     | 129                                    | 24                                    |
| Race/Ethnicity (N):                      |  |                                       |
| Black                                    | 129                                    | 23                                    |
| White                                    | 14                                     | 0                                     |
| Hispanic                                 | 11                                     | 2                                     |
| Other                                    | 8                                      | 0                                     |
| Occupation (N):                          |  |                                       |
| Healthcare worker                        | 7                                      | 0                                     |
| First responder                          | 2                                      | 0                                     |
| Restaurant industry                      | 12                                     | 1                                     |
| Grocery store                            | 6                                      | 0                                     |
| Other/unemployed                         | 135                                    | 24                                    |
| Basal Metabolic Index (N):               |  |                                       |
| <18.5                                    | 4                                      | 0                                     |
| 18.5 – 24.9                              | 56                                     | 5                                     |
| 25 – 29.0                                | 48                                     | 7                                     |
| >30                                      | 53                                     | 13                                    |
| Mean CD4 (Cell/ul, IQR)                  | 641 (393-879)                          | 595 (389-93)                          |
| Median HIV-1 viral load (Copies/ml, IQR) | <20 (0)                                | <20 (0-50)                            |
| Known Exposure to COVID-19 (N)           | 21                                     | 3                                     |
| COVID-19 PCR Performed (N):              |  |                                       |
| Positive PCR, Symptomatic                | 9                                      | 8                                     |
| Negative PCR, Symptomatic                | 16                                     | 3                                     |
| PCR not performed, Symptomatic           | 13                                     | 3                                     |

**629 SEROPREVALENCE OF ANTIBODIES AGAINST SARS-CoV-2 AMONG PEOPLE LIVING WITH HIV (PLWH)**

**Smitha Gudipati<sup>1</sup>, Monica Lee<sup>1</sup>, Megan Scott<sup>1</sup>, Sean Yape<sup>1</sup>, Nicholas Yared<sup>1</sup>, Indira Brar<sup>1</sup>, Joanne Huisting<sup>1</sup>, Norman Markowitz<sup>1</sup>**  
<sup>1</sup>Henry Ford Hospital, Detroit, MI, USA

**Background:** COVID-19 first reported in the US on 1/2020 is a global pandemic. In PLWH, COVID-19 outcomes have been reported to be similar or worse compared to the general population; however, the seroprevalence in this group has not been identified. As of 6/2020, 2.7% of the 960 PLWH in our Ryan-White (RW) clinic have tested PCR+ for COVID-19. Yet, these likely represent only a fraction of COVID-19 infections, as an unknown proportion of cases are mild or asymptomatic and not diagnosed. Our goal was to estimate the seroprevalence in our RW patients (pts), irrespective of known past COVID-19 infection. The RW program funds HIV care for a diverse group impacted by a number of social determinants of health, including low socioeconomic status.

**Methods:** We conducted a seroprevalence study, which recruited pts in the RW program at Henry Ford Hospital. All RW pts were offered participation during clinic visits. After informed consent, pts completed a survey and had blood sampled for COVID-19 antibody using the Beckman Coulter Access SARS-CoV-2 IgG assay. Pts' electronic medical records were reviewed for demographic clinical features, including previous COVID-19 testing. The study was IRB approved.

**Results:** 187 PLWH were enrolled from 9/2020-11/2020 (Table 1). Median age: 46 (IQR: 34-57); 153 males; 152 black; 24 reported a previous COVID-19 exposure; 66 had a BMI of  $\geq 30$ . Mean CD4 count was 629.5 (IQR: 390-859), and 129 pts were HIV suppressed. 17 had PCR-confirmed COVID-19, and 16 reported symptoms consistent with COVID-19 but with unconfirmed diagnoses. Of 187 PLWH, 25 (13%) were COVID-19 IgG+ of whom 8 were previously PCR+. 9/17 PLWH who were PCR+ for COVID-19 were COVID-19 IgG negative at a mean of 7 months from the initial PCR test.

**Conclusion:** The COVID-19 seroprevalence of 13% reported in this study of PLWH in our clinic was about 5-fold greater than the number of reported cases by PCR+ in the same population. This estimate of past infection is also an underestimate given the absence of antibody at the time of the serological testing in 53% of PLWH with documented PCR+ infection and the likelihood of infection in some of those never tested. Conversely, the impact of health disparities on the RW pts likely increases the chance of acquisition of COVID-19 compared to other populations. In order to better understand the penetration of COVID-19 into the PLWH community, a greater understanding of the dynamics of the antibody response to COVID-19 is needed.

**630 SUSTAINED SEROPREVALENCE IN HEALTH CARE WORKERS AT A QUATERNARY CENTER, NEW YORK CITY**

**Delivette Castor<sup>1</sup>, Jason Zucker<sup>1</sup>, Brit Sovic<sup>1</sup>, Marvin Castellon<sup>1</sup>, Deborah Theodore<sup>1</sup>, Jennifer Chang<sup>1</sup>, Shaoyi Zhang<sup>1</sup>, Meredith McNairy<sup>1</sup>, Sade Tukuru<sup>1</sup>, Rusty Greene<sup>1</sup>, Steven Palmer<sup>1</sup>, Xiomara Javier-Espinal<sup>1</sup>, Yumeng Wu<sup>1</sup>, Kathrine Meyers<sup>1</sup>, Magdalena Sobieszczyk<sup>1</sup>, for the Clinical Trials Unit**  
<sup>1</sup>Columbia University Medical Center, New York, NY, USA

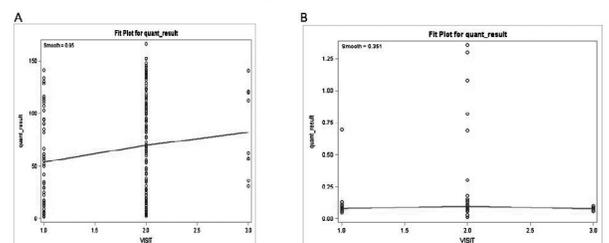
**Background:** Health care workers (HCWs) remain disproportionately affected by COVID-19. They experience higher transmission rates of SARS-CoV-2, and the extent, duration and pattern of antibody response remains under examined. The correlates of serological patterns are also unclear. We examined longitudinal SARS-CoV-2 sero-patterns and their correlates among a cohort of HCW.

**Methods:** HCWs (N=465) were recruited at a large quaternary medical center in New York City and followed prospectively with bi-monthly assessments of the following; demographic characteristics, COVID-19 exposure in the work, home and community settings, and molecular and antibody COVID-19 laboratory tests including quantitative measurements of antibody titers. Baseline and longitudinal patterns in antibody response and titers over the first 4 months were used to characterize HCW who remained persistently seronegative, seropositive, those who acquired and lost seropositivity and those with variable seropositivity. Chi-square test for the association of seropattern correlates and loess regression was used to examine longitudinal trends.

**Results:** Baseline seropositivity was 32.6% (N=148/465), 34.6% (N=153/441) at month 2 and 38.3% (N=125/326) by month 4. Exactly 63.9%, 27.3%, 1.5%, 1.5% and 5.7% of HCW tested overall were persistently seronegative, persistently seropositive, became positive after baseline, lost seropositivity and had variable positivity, respectively. Among seropositive HCW, mean antibody levels increased from 53.7 at baseline to 69.8 at month 2 and 82.9 at month 4 (figure 1). Factors significantly associated with being ever seropositive were, history of prior COVID-19 testing, household member testing COVID-19 positive, whether there were other essential employees in the home, and history or current symptoms. We also observed an association with contact of suspected or confirmed co-worker as significantly higher among HCW who were persistently positive (24.5%), incident seropositives (33.3%) and variable seropositivity (52.2%) than those who were persistently negative (19.9%) or lost seropositivity (16.7%).

**Conclusion:** HCWs exposure risks continue to persist in the workplace and in the home. We observed few positive molecular tests, suggesting few transmission, but these exposure may potentially sustain seropositivity. These findings are preliminary and need to be further investigated.

**Figure 1. Loess regression curve of change in antibody levels among seropositive (A) and seronegative (B) health care providers in NYC.**



**631 OVERCROWDED HOUSING INCREASES RISK FOR COVID-19 MORTALITY: AN ECOLOGICAL STUDY**

**Karan Varshney**<sup>1</sup>, Jenna Adalbert<sup>2</sup>

<sup>1</sup>Vancouver Coastal Health, Vancouver, Canada, <sup>2</sup>Thomas Jefferson University, Philadelphia, PA, USA

**Background:** The 2019-novel coronavirus (COVID-19) has devastated the United States (US) population and has exacerbated existing health inequalities. Those residing in areas of high population density are at an elevated risk, suggesting that residence in an overcrowded household may result in heightened vulnerability. However, as the association between residing in an overcrowded household and risk of mortality from COVID-19 is unknown, the purpose of this study was to analyze this relationship.

**Methods:** COVID-19 data was acquired for each of the 85 cities in Los Angeles County, the region with the highest number of recorded cases in the US, along with data on housing and demographics. Overcrowded households were defined as having 1.0+ persons per room. Bivariate regression was performed between the number of overcrowded households and the number of COVID-19 deaths. Backwards stepwise linear regression was then conducted with risk factors for COVID-19 mortality as potentially eligible input variables. Collinearity was assessed by considering the variance inflation factors (VIF); variables with high collinearity (VIF above 8) were removed.

**Results:** Bivariate regression indicated that the number of overcrowded households was positively associated with the number of COVID-19 deaths (standardized  $\beta = 0.844$ ,  $p < 0.001$ ). COVID-19 case totals, number of individuals aged 60 or above, and number of overcrowded households met conditions for inclusion in the backwards stepwise linear regression model. This analysis revealed that all three of these independent variables were positively associated with number of deaths, with the largest effect being seen with overcrowded housing (standardized  $\beta = 0.386$ ,  $p = 0.001$ ), followed by number of cases (standardized  $\beta = 0.307$ ,  $p = 0.014$ ), and number of individuals aged 60+ (standardized  $\beta = 0.282$ ,  $p < 0.001$ ).

**Conclusion:** Overcrowded housing was found to be a major risk factor for COVID-19 mortality in this study and served as a better predictor of number of deaths than the number of people 60+, and even the total number of COVID-19 cases. These findings have important implications for addressing the COVID-19 pandemic. While age and comorbidities have frequently been described as risk factors for poor outcomes, these findings indicate a critical need for COVID-19 control efforts to more thoroughly assess for overcrowded housing. Furthermore, the striking absence of research on overcrowded housing indicates a clear direction for future studies.

**632 DYNAMICS OF THE COVID-19 EPIDEMIC AT THE CALIFORNIA-MEXICO BORDER**

**Bram Vrancken**<sup>1</sup>, Simon Dellicour<sup>1</sup>, Sanjay R. Mehta<sup>2</sup>, Steffanie Strathdee<sup>2</sup>, Davey M. Smith<sup>2</sup>, Antoine Chaillon<sup>3</sup>

<sup>1</sup>KU Leuven, Leuven, Belgium, <sup>2</sup>University of California San Diego, La Jolla, CA, USA, <sup>3</sup>University of California San Diego, San Diego, CA, USA

**Background:** As countries around the world review interventions for containing the COVID-19 pandemic, movement of populations has been identified as a key factor of viral dispersal and limiting the population flow intensity has been applied to contain the current COVID-19 epidemic. Evolutionary analyses of well-annotated sequencing data can provide insights into viral transmission dynamics. Herein, we characterized the dynamics of COVID-19 transmission within California and across the Mexico-California (MX/CA) border, the busiest land border-crossing area in the world, to inform the containment policy in this binational context.

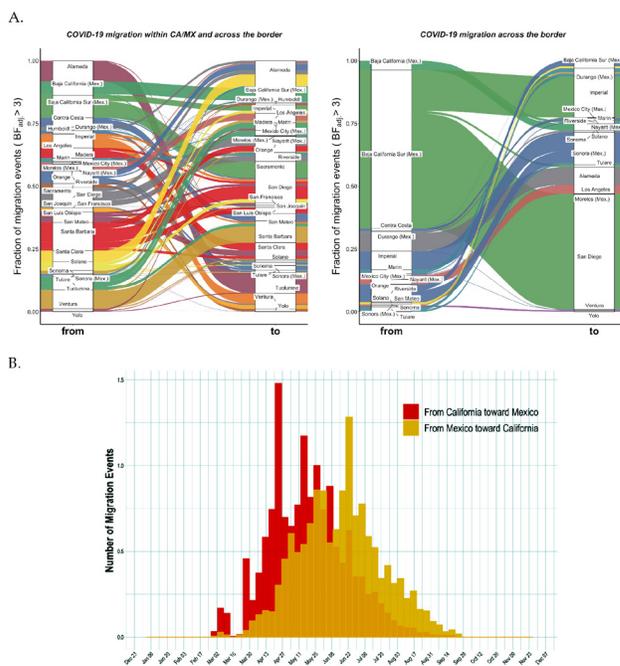
**Methods:** All publicly available SARS-CoV-2 full genome sequences (human host) available on the GISAID database were collected (as of Nov. 16th, 2020). After sequence curation, a multistep phylogenetic approach was applied to identify putative clusters of transmission within CA (across counties), MX (across states) and across the MX/CA border. These clades were analyzed with a discrete phylogeographic model to evaluate transmission dynamics of COVID-19 in the MX/CA region.

**Results:** From a total of 174,324 SARS-CoV-2 sequences including 5,471 sequences from Mexico (7 States,  $n=223$ )/California (29 counties,  $n=5,248$ ), we identified 622 unique introduction events into the study region, including 381 clusters of size  $\geq 3$  from  $\geq 2$  locations (i.e. CA county and/or MX state). Of these, 339 (89%) clusters were from CA only across 23 counties, 5 (1.3%) were from MX only across 6 states and 38 (10%) included sequences from both CA and MX.

Discrete phylogeographic analysis revealed a complex viral migration network within CA/MX and across the border (Figure 1A, left panel). Analyses of the 38 clusters including sequences from CA and MEX showed bidirectional migration events across the border (Figure 1B). In particular we showed migration events in the border region from the border state of Baja California, MX to the border county of San Diego, CA and from the border county of Imperial County, CA to the border state of Sonora, MX (Figure 1A, right panel).

**Conclusion:** This comprehensive analysis of all publicly available COVID-19 sequences showed local transmission across regions within CA and MX as well as across neighboring locations across the border. Similar to the 2009 H1N1 pandemic, the MX/CA border does not appear to be a major barrier to the spread of COVID-19, necessitating coordinated transnational intervention approaches.

**Figure 1. A.** Relative contribution of California counties and Mexico States to the spread of COVID-19 in the border region. Results accounting for migration links associated with an adjusted Bayes factor ( $BF_{adj} \geq 3$ ). The Sankey plot represents the proportion of migration events from each source risk group ('from') toward the recipient risk group ('to'). **B.** Number of introductions into California from Mexico and into T Mexico from California.



**633 A DESCRIPTION AND ANALYSIS OF COVID-19 IN A POPULATION-REPRESENTATIVE COHORT**

**Yannis Herrmann**<sup>1</sup>, Tim Starck<sup>1</sup>, Niall Brindl<sup>1</sup>, Philip J. Kitchen<sup>1</sup>, Lukas Raedeker<sup>1</sup>, Jakob Sebastian<sup>1</sup>, Lisa Koepfel<sup>1</sup>, Frank Tobian<sup>1</sup>, Aurélie Souares<sup>1</sup>, André Mihaljevic<sup>1</sup>, Uta Merle<sup>1</sup>, Theresa Hippchen<sup>1</sup>, Felix Herth<sup>1</sup>, Andreas Welker<sup>2</sup>, Claudia Denking<sup>1</sup>

<sup>1</sup>Heidelberg University, Heidelberg, Germany, <sup>2</sup>Landratsamt Rhein-Neckar, Heidelberg, Baden-Wuerttemberg, Germany

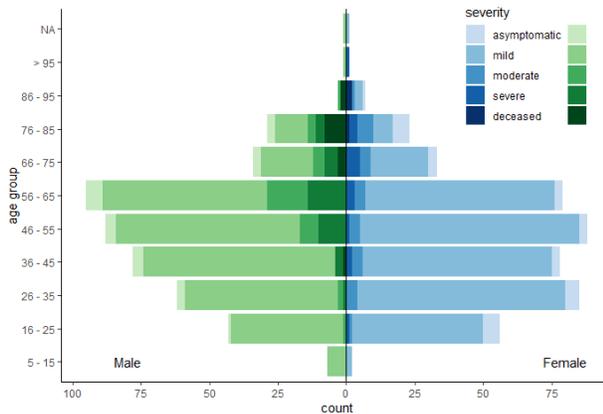
**Background:** Most data on COVID-19 was collected in hospitalized cases. Much less is known about the spectrum of disease in entire populations including non-hospitalized patients and minors. In this study, we examine a representative cohort in an administrative district in Southern Germany who tested positive for SARS-CoV-2 between February and June of 2020.

**Methods:** We contacted all confirmed SARS-CoV-2 cases in an administrative district in southern Germany. Consenting participants answered a retrospective survey either via a telephone, electronically or via mail. Clinical and sociodemographic features were compared between hospitalized and non-hospitalized patients. Additionally, we assessed potential risk factors for hospitalization and time to hospitalization in a series of regression models. As predictors we assessed age as a continuous variable, sex, smoking as a continuous variable using pack years, living with children (age <18), hypertension (yes/no), coronary heart disease (CHD; yes/no), diabetes (type 1 or type 2; yes/no) and lung conditions (yes/no). Lung conditions were defined as a combined variable of either COPD, asthma treated with medications, any other lung disease or previously performed lung surgery. Secondly, we estimated

the influence of the same covariates on the time from symptom onset to hospitalization with a Cox proportional hazard ratio (HR) model.

**Results:** We included 897 participants in our study, 69% out of 1,305 total cases in the district with a mean age of 47 years (range 2-97), 51% of which were female and 47% had a pre-existing illness. The percentage of asymptomatic, mild (symptomatic, no hospitalization), moderate (leading to hospital admission) and critical illness (requiring mechanical ventilation) was 54 patients (6%), 713 (79%), 97 (11%) and 16 (2%), respectively. Seventeen patients (2%) died. The most prevalent symptoms were fatigue (65%), cough (62%) and dysgeusia (60%). The risk factors for hospitalization included older age (OR 1.05 per year increase; 95% CI 1.04-1.07) preexisting lung conditions (OR 3.09; 95% CI 1.62-5.88). Female sex was a protective factor (OR 0.51; 95% CI 0.33-0.77).

**Conclusion:** This population-representative analysis of COVID-19 cases confirms age, male sex and preexisting lung conditions but not cardiovascular disease as risk factors for severe illness. Almost 80% of infection take a mild course, whereas 13% of patients suffer moderate to severe illness.



fever and loss of smell or taste were reported in 13% and 10% of individuals, respectively. Most COVID-19 cases in both symptom groups reported not adhering to social distancing guidelines.

**Conclusion:** Based on preliminary data, asymptomatic SARS-CoV-2 infection in Malawians visiting HFs was relatively rare. This suggests a need for continued surveillance to ensure a better understanding of exposures as well as further monitoring of SARS-CoV-2 transmission in Malawi.

Table 1: Characteristics of Symptomatic and Asymptomatic Participants by SARS-CoV-2 Status

| Characteristic  | Symptomatic (N = 1300)   |                          |         | Asymptomatic (N = 6648)  |                          |         |
|---|--------------------------|--------------------------|---------|--------------------------|--------------------------|---------|
|   | COVID 19 positive (n, %) | COVID 19 negative (n, %) | p value | COVID 19 positive (n, %) | COVID 19 negative (n, %) | p value |
| <b>Total</b>  | 30 (2%)                  | 1270 (98%)               |         | 37 (1%)                  | 6611 (99%)               |         |
| <b>Age</b>  |                          |                          |         |                          |                          |         |
| 5-14  | 1 (3%)                   | 55 (4%)                  | 0.04    | 0 (0%)                   | 92 (1%)                  | 0.88    |
| 15-49   | 20 (67%)                 | 1042 (82%)               |         | 34 (92%)                 | 5790 (88%)               |         |
| 50+   | 9 (30%)                  | 173 (14%)                |         | 3 (8%)                   | 711 (11%)                |         |
| <b>Sex*</b>   |                          |                          |         |                          |                          |         |
| Male  | 14 (47%)                 | 504 (40%)                | 0.44    | 16 (43%)                 | 1830 (28%)               | 0.04    |
| Female  | 16 (53%)                 | 766 (60%)                |         | 21 (57%)                 | 4778 (72%)               |         |
| <b>Region</b>   |                          |                          |         |                          |                          |         |
| Central   | 14 (47%)                 | 661 (52%)                | 0.57    | 19 (51%)                 | 3412 (52%)               | 0.65    |
| Northern  | 11 (37%)                 | 473 (37%)                |         | 17 (46%)                 | 2790 (42%)               |         |
| Southern  | 5 (17%)                  | 136 (11%)                |         | 1 (3%)                   | 409 (6%)                 |         |
| <b>Residence*</b>   |                          |                          |         |                          |                          |         |
| Urban   | 18 (60%)                 | 654 (52%)                | 0.36    | 26 (70%)                 | 3496 (53%)               | 0.03    |
| Rural   | 12 (40%)                 | 615 (48%)                |         | 11 (30%)                 | 3113 (47%)               |         |
| <b>Close contact</b>  |                          |                          |         |                          |                          |         |
| Yes, contact with confirmed                                     | 2 (7%)                   | 11 (1%)                  | 0.03    | 0 (0%)                   | 24 (0%)                  | 0.79    |
| Yes, suspected contact  | 1 (3%)                   | 44 (3%)                  |         | 0 (0%)                   | 89 (1%)                  |         |
| No, contact tested neg  | 0 (0%)                   | 4 (0%)                   |         | 0 (0%)                   | 25 (0%)                  |         |
| No  | 21 (70%)                 | 1074 (85%)               |         | 33 (89%)                 | 5923 (90%)               |         |
| Don't Know/ Refused   | 6 (20%)                  | 137 (11%)                |         | 4 (11%)                  | 555 (8%)                 |         |
| <b>Travel outside country*</b>                                  |                          |                          |         |                          |                          |         |
| Yes   | 1 (3%)                   | 13 (1%)                  | 0.06    | 1 (3%)                   | 27 (0%)                  | 0.16    |
| No  | 28 (93%)                 | 1251 (99%)               |         | 36 (97%)                 | 6548 (99%)               |         |
| Missing   | 1 (3%)                   | 6 (0%)                   |         | 0 (0%)                   | 36 (1%)                  |         |
| <b>Behavior among those who received an adult questionnaire</b> |                          |                          |         |                          |                          |         |
| <b>Stopped going to health facility</b>                         |                          |                          |         |                          |                          |         |
| Yes   | 4 (13%)                  | 117 (9%)                 | 0.68    | 9 (24%)                  | 668 (10%)                | 0.04    |
| No  | 25 (83%)                 | 1102 (87%)               |         | 28 (76%)                 | 5832 (88%)               |         |
| Don't Know/ Refused   | 1 (3%)                   | 51 (4%)                  |         | 0 (0%)                   | 111 (2%)                 |         |
| <b>Avoid large gathering</b>                                    |                          |                          |         |                          |                          |         |
| Yes   | 11 (37%)                 | 362 (29%)                | 0.62    | 15 (41%)                 | 2115 (32%)               | 0.43    |
| No  | 18 (60%)                 | 858 (68%)                |         | 21 (57%)                 | 4396 (66%)               |         |
| Don't Know/ Refused   | 1 (3%)                   | 50 (4%)                  |         | 1 (3%)                   | 100 (2%)                 |         |
| <b>Avoid places of worship</b>                                  |                          |                          |         |                          |                          |         |
| Yes   | 11 (37%)                 | 316 (25%)                | 0.34    | 15 (41%)                 | 1812 (27%)               | 0.16    |
| No  | 18 (60%)                 | 905 (71%)                |         | 21 (57%)                 | 4697 (71%)               |         |
| Don't Know/ Refused   | 1 (3%)                   | 49 (4%)                  |         | 1 (3%)                   | 102 (2%)                 |         |
| <b>Avoid using public transportation</b>                        |                          |                          |         |                          |                          |         |
| Yes   | 7 (23%)                  | 220 (17%)                | 0.49    | 15 (41%)                 | 1373 (21%)               | 0.01    |
| No  | 21 (70%)                 | 1000 (79%)               |         | 22 (59%)                 | 5131 (78%)               |         |
| Don't Know/ Refused   | 2 (7%)                   | 50 (4%)                  |         | 0 (0%)                   | 107 (2%)                 |         |

\*Values in % were also provided outside the country. If the participant is asymptomatic identify 14 days in a survey date or 14 days before onset (if applicable). If the participant was symptomatic refer to 14 day period date: symptom onset.

\* Fisher's exact test was used for all values < .05.

**634 SARS-CoV-2 SURVEILLANCE IN 14 HEALTH FACILITIES IN MALAWI**  
 Karam Sachathep<sup>1</sup>, Felix Kayigamba<sup>2</sup>, Lyson Tenthani<sup>2</sup>, Francis M. Ogollah<sup>2</sup>, Katherine Yuengling<sup>1</sup>, Giles Reid<sup>1</sup>, Gili Hrusa<sup>1</sup>, Mathew Kagoli<sup>3</sup>, Anne Chauma-Mwale<sup>3</sup>, Andrew F. Auld<sup>4</sup>, Evelyn Kim<sup>4</sup>, Nellie Wadonda<sup>4</sup>, Alinune Kabaghe<sup>4</sup>, Daniel Payne<sup>4</sup>, Tiffany G. Harris<sup>1</sup>

<sup>1</sup>ICAP at Columbia University, New York, NY, USA, <sup>2</sup>ICAP, Lilongwe, Malawi, <sup>3</sup>Public Health Institute, Lilongwe, Malawi, <sup>4</sup>Centers for Disease Control and Prevention, Lilongwe, Malawi

**Background:** As of October 26, 2020, Malawi reported 5,894 confirmed COVID-19 cases with 183 deaths. A state of disaster was declared in March; however, a strict lockdown order was never issued. Malawi has implemented a testing strategy involving screening and testing only symptomatic persons due to limited availability of tests. Sentinel surveillance was conducted with the primary purpose of estimating the prevalence of symptomatic and asymptomatic SARS-CoV-2 infection among children >5 years and adults in Malawi health facilities (HF).

**Methods:** SARS-CoV-2 surveillance was conducted at 14 purposively selected HFs across 8 districts in all 3 regions of Malawi from August 27 to October 14, 2020. Persons entering HFs were screened for COVID-19 symptoms; all those with symptoms suggestive of COVID-19 per Malawi guidelines and a systematic sample of asymptomatic individuals were invited to participate. Questionnaire data and nasopharyngeal swabs were collected from consenting persons. Infection was confirmed by SARS-CoV-2 RT-PCR assay (Abbott m2000). This preliminary analysis was restricted to those with test results. We performed chi-square tests to assess bivariate associations between demographic or behavioral characteristics and SARS-CoV-2 status stratified by symptom status.

**Results:** A total of 8,169 (1,350 symptomatic, 6,819 asymptomatic) individuals were enrolled. Results are currently available for 1,300 (96%) symptomatic and 6,648 (97%) asymptomatic participants. A total of 30 (2%) symptomatic and 37 (0.6%) asymptomatic participants tested SARS-CoV-2 positive (Table). Most (67%) positive symptomatic participants were aged 15-49 years, followed by 50+ years (30%); a similar trend was seen for asymptomatic cases. A higher percentage of symptomatic cases reported being in contact with a confirmed or suspected COVID-19 case than symptomatic non-cases (p=.03). Among positive symptomatic individuals, the most common symptom was cough (70%);

**635 SARS-CoV-2 TRANSMISSION AMONG FIRST CASES AND THEIR CONTACTS IN KISUMU COUNTY, KENYA**

Margaret Mburu<sup>1</sup>, Jayne L. Kulzer<sup>2</sup>, Norton M. Sang<sup>1</sup>, Amy Herman-Roloff<sup>3</sup>, Beth T. Barr<sup>3</sup>, Francesca Odhiambo<sup>1</sup>, Edwin Mulwa<sup>1</sup>, Benard Awuonda<sup>1</sup>, Albert M. Odhiambo<sup>4</sup>, Clayton Onyango<sup>3</sup>, Rachael Joseph<sup>3</sup>, Aoko Appolonia<sup>3</sup>, Craig Cohen<sup>2</sup>, Elizabeth A. Bukusi<sup>1</sup>, Pamela Murnane<sup>2</sup>

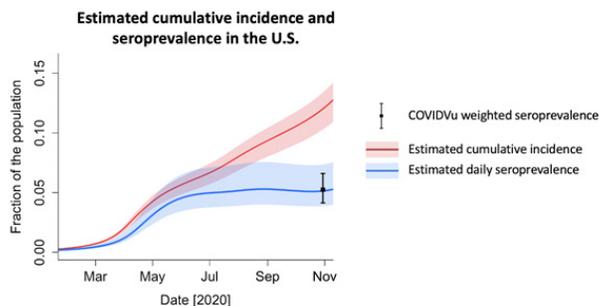
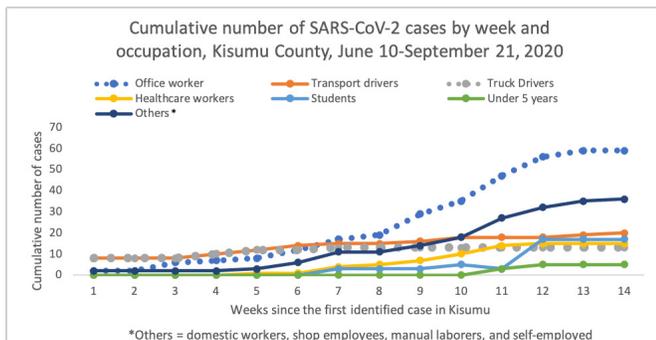
<sup>1</sup>Kenya Medical Research Institute, Nairobi, Kenya, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA, <sup>3</sup>US Centers for Disease Control and Prevention, Nairobi, Kenya, <sup>4</sup>Kisumu County Department of Health, Kisumu, Kenya

**Background:** To inform epidemic control strategies in Kisumu County, Kenya, we examined exposures and presumed routes of SARS-CoV-2 transmission among the first identified cases and their contacts in the county.

**Methods:** Between June 10, 2020 and September 21, 2020, we enrolled the first identified SARS-CoV-2 PCR positive cases in Kisumu County. Across the enrollment period, strict shelter-in-place and curfew mandates were gradually loosened. Enrolled cases were asked to identify all persons who were within 2 meters of them, between 48 hours prior to symptoms through the time of the enrollment interview; multiple attempts were made to reach and enroll each named contact. All cases and contacts answered detailed questionnaires about recent potential exposures at enrollment and 2 weeks later. Contacts with SARS-CoV-2 PCR positive tests at either visit were enrolled as "secondary" cases and presumed to have acquired infection from the index case who named them as a contact.

**Results:** We enrolled 152 cases (125 index and 27 secondary) cases and 248 contacts, including 27 contacts (11%) who acquired infection and also enrolled as secondary cases. Among all cases, 59% were male and the median age was 35 years (interquartile range [IQR] 28, 44). Among contacts, 51% were male and the median age was 24 years (IQR 11.2, 35.2). While the earliest identified SARS-CoV-2 infections in Kisumu County were among truck drivers, as others started returning to work, community transmission escalated. Within 3 months from the first identified case in the county, office workers represented the largest occupation category among cases (37%) (Figure). A total of 12 index cases (10%) transmitted to the 27 contacts who acquired infection. Among these 27 secondary cases, 85% were household members of index cases and 48% were <15 years old.

**Conclusion:** Within 3 months from the first identified case of SARS-CoV-2 infection in Kisumu County, office workers had the highest risk of infection, suggesting a need for more rigorously applied physical distancing and masking policies as employees of non-essential services return to work. While transmission from cases to contacts was relatively low, the vast majority occurred within households and children were disproportionately represented among secondary cases. Enhanced support for within-household distancing during the isolation of cases may be needed. Given the concurrent increase in office-worker infections, undetected community transmission outside our enrolled cohort likely occurred.



**636 CUMULATIVE INCIDENCE OF SARS-CoV-2 INFECTION AND EPIDEMIC METRICS, UNITED STATES**

**Patrick S. Sullivan**<sup>1</sup>, Kayoko Shioda<sup>1</sup>, Eric Hall<sup>1</sup>, Heather Bradley<sup>2</sup>, Nicole Luisi<sup>1</sup>, Kristen Nelson<sup>1</sup>, Travis Sanchez<sup>1</sup>, Mariah Valentine-Graves<sup>1</sup>, Mansour Fahimi<sup>3</sup>, Rich Rothenberg<sup>2</sup>, Ben Lopman<sup>1</sup>, Aaron J. Siegler<sup>1</sup>, for the COVIDVU Study Group  
<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Georgia State University, Atlanta, GA, USA, <sup>3</sup>Marketing Systems Group, New York, NY, USA

**Background:** Understanding the cumulative incidence of SARS-CoV-2 infections in the United States has been limited by asymptomatic infections, waning antibodies after natural infection, incomplete case ascertainment and reporting, and limited representative samples. We conducted a probability survey of US households to measure SARS-CoV-2 infection and immune response and to estimate the cumulative incidence of SARS-CoV-2 infection.

**Methods:** A multistage random sample of US postal addresses were mailed a kit to self-collect an anterior nares swab and a dried blood spot (DBS) sample from August to December 2020. Specimens were tested by EUA-approved PCR and serology tests. Weighted estimates of antibody prevalence, together with historical patterns of antibody waning, were used to estimate the cumulative incidence of SARS-CoV-2 infections, the diagnosed fraction, and infection fatality ratio (IFR). Weighted estimates were used to calculate prevalence ratios comparing demographic, geographic, and clinical subgroups.

**Results:** 37,056 kits were mailed to sampled US households. Overall, 5,666 surveys were completed by December 8, 2020; of these, 4,654 also returned a DBS specimen with a valid antibody result. Overall participation rate was 11.8%. We estimated 39,421,841 (95% credible interval (CrI): 33,759,801-43,958,068) total infections by October 30, 2020, an estimated diagnosed fraction of 17% (95% CrI: 15-21%) and an estimated IFR of 0.64% (95% CrI: 0.58-0.75%). Daily seroprevalence peaked by Sept 2020 and remained stable through November 2020 due to a balance of waning antibodies and new infections (Figure). Non-Hispanic Black (PR: 2.2; 95% confidence interval (CI): 1.2-4.0) and Hispanic (PR: 3.1, CI: 1.8-5.3) respondents were more likely than White non-Hispanic to have laboratory evidence of prior SARS-CoV-2 infection. Prevalence was also higher among those living in metropolitan areas (PR vs non-metropolitan areas: 2.5, CI: 1.3-5.0) and among those reporting cold or flu symptoms (PR: 2.6, CI: 1.6-4.1) or loss of taste or smell (PR: 12.8, CI: 8.5-19.4) since January 1, 2020.

**Conclusion:** We report the results of the first national probability sample of US households to assess the prevalence of antibodies to SARS-CoV-2 and cumulative incidence. As of October 30, 2020, about 1 in 8 US residents aged ≥18 years had been infected with SARS-CoV-2, and about 1 in 6 of those had been diagnosed. Household-based probability surveys provide a minimally biased benchmark to characterize epidemic dynamics.

**637 RECENT SARS-CoV-2 SEROCONVERSION IN A NATIONAL PROSPECTIVE COHORT OF US ADULTS**

**Denis Nash**<sup>1</sup>, Madhura S. Rane<sup>1</sup>, Mindy Chang<sup>1</sup>, Sarah G. Kulkarni<sup>1</sup>, William X. You<sup>1</sup>, Rebecca Zimba<sup>1</sup>, Amanda Berry<sup>1</sup>, Chloe Mirzayi<sup>1</sup>, Shivani Kochhar<sup>1</sup>, Andrew Maroko<sup>1</sup>, McKaylee M. Robertson<sup>1</sup>, Drew A. Westmoreland<sup>1</sup>, Angela Parcesepe<sup>2</sup>, Christian Grov<sup>1</sup>

<sup>1</sup>Institute for Implementation Science in Population Health (ISPH), City University of New York (CUNY), New York, NY, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

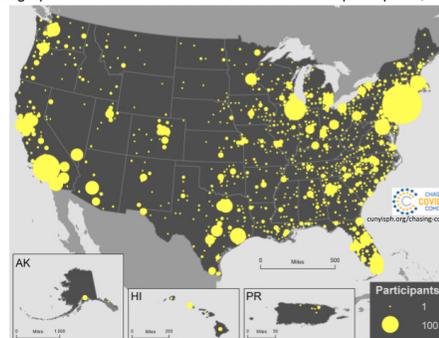
**Background:** Epidemiologic risk factors for SARS-CoV-2 infection are best characterized via prospective cohort studies, complementing case-based surveillance and cross-sectional seroprevalence studies.

**Methods:** We estimated the cumulative incidence of SARS-CoV-2 infection and incidence rates of seroconversion in a national prospective online cohort of 6745 US adults, enrolled during March-July 2020. A subset (n=4459) underwent serologic testing (Bio-Rad Platelia Total Ab, IgA/IgM/IgG), offered initially during May-Sept. 2020 and again in Nov. 2020-Jan. 2021.

**Results:** A total of 303 of 4459 individuals showed serologic evidence of past SARS-CoV-2 infection (6.8%, 95%CI 6.1-7.6%). Among 3280 initially seronegative participants who had a subsequent serologic test, there were 145 seroconversions over 1562 person-years of follow-up (incidence rate=9.3 per 100 person-years [95%CI 7.9-11.0]). Racial/ethnic disparities in crude incidence rates were apparent through Jan. 2021 (rate ratio [RR]Hispanic v White)=2.1, 95%CI 1.4-3.1; RRNon-Hispanic Black v White=1.8, 95%CI 0.96-3.1). Incidence was higher in the southern (RRSouth v Northeast=1.7, 95%CI 1.1-2.8) and midwest (RRmidwest v Northeast=1.6, 95%CI 0.98-2.7) regions, in rural v urban areas (RR=1.5, 95%CI 1.0-2.2), and among essential workers (RR=1.7, 95%CI 1.1-2.5). Household crowding (RR=1.6, 95%CI 1.1-2.3), indoor restaurant dining (RR=2.0, 95%CI 1.4-2.8), visiting places of worship (RR=2.0, 95%CI 1.3-2.9), wearing masks sometimes (v always) while grocery shopping (RR=2.5, 95%CI 1.3-4.4), not wearing masks when visiting people outside the household (RRsometimes v always=1.3, 95%CI 0.88-2.1; RRnever v always=2.0, 95%CI 1.2-3.2), gathering in groups of >10 (RRindoors v never=1.74, 95%CI 1.2-2.5; RRoutdoors v never=1.8, 95%CI 1.3-4.3), and recent air travel (RR=1.7, 95%CI 1.1-2.6) were associated with higher incidence. Among 303 seropositive persons, 27.4% had asymptomatic infections and 32% reported a positive SARS-CoV-2 PCR test or provider diagnosis. There were major gaps in the uptake of public health interventions aimed at isolation (31%) and contact tracing (asked about contacts [18%]; told about exposure to a case [7.6%]).

**Conclusion:** Modifiable risk factors and low uptake of public health strategies drive SARS-CoV-2 transmission across the US. It is critical to address inequities in incidence, reduce risk factors, and improve the reach of public health strategies.

Geographic distribution of CHASING COVID Cohort participants, N=6,745



### 638 US POPULATION-BASED SURVEY OF VACCINE WILLINGNESS AND SARS-CoV-2 ANTIBODY PREVALENCE



**Aaron J. Siegler**<sup>1</sup>, Eric Hall<sup>1</sup>, Travis Sanchez<sup>1</sup>, Heather Bradley<sup>2</sup>, Nicole Luisi<sup>1</sup>, Kristen Nelson<sup>1</sup>, Mariah Valentine-Graves<sup>1</sup>, Mansour Fahimi<sup>3</sup>, Kayoko Shioda<sup>1</sup>, Ben Lopman<sup>1</sup>, Rich Rothenberg<sup>2</sup>, Patrick S. Sullivan<sup>1</sup>, for the COVIDVu Study Group  
<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>Georgia State University, Atlanta, GA, USA, <sup>3</sup>Marketing Systems Group, Horsham, PA, USA

**Background:** Developing representative estimates of COVID-19 vaccine acceptance will be essential to public health planning as the vaccine supply moves towards sufficiency in meeting initial levels of demand. We conducted a national probability household survey to assess vaccine willingness and history of SARS-CoV-2 infection based on antibody response.

**Methods:** Study materials were sent to an address-based sample frame that includes nearly all residential addresses in the US. Participants completed a behavioral survey and dried blood spot (DBS) specimen collection for SARS-CoV-2 antibody testing during the study period, August 9 – December 8, 2020. Vaccine willingness was measured with a 5-point Likert scale item with responses ranging from "Very unlikely" to "Very likely." Sample weights were calculated and applied to descriptive statistics and prevalence ratios (PR). We categorized persons as either Ig negative, Ig positive and aware of prior COVID-19 infection, or Ig positive and unaware of prior COVID-19 infection.

**Results:** A total of 4,654 respondents completed the survey and had a valid antibody test result, representing 242,875,582 US adults. Overall, a substantial proportion, 32% (76,967,749 adults), were unsure or unwilling to receive a COVID-19 vaccine. Many groups at increased risk for SARS-CoV-2 had higher proportions unsure or unwilling, including Black (46%) relative to White (30%,  $p < .001$ ) race, persons working outside home (38%) relative to at home (21%,  $p < .001$ ), and smokers (44%) relative to nonsmokers (29%,  $p < .001$ ) (Table 1). Dissonance between transmission risk and vaccine willingness was also observed in biologic data. Persons Ig positive (previously infected) and unaware of their status had a higher point estimate of unwillingness to be vaccinated (39%) than persons Ig negative with no history of infection (31%,  $p = .28$ ). Overall, we estimate 12% (29,241,030 adults) were very unlikely to be vaccinated, 7% (15,729,748) were somewhat unlikely, 13% (31,996,971) were unsure, 19% (44,958,518) were likely, and 50% (119,820,865) were very likely. **Conclusion:** In the first national probability survey with biomarker data, we demonstrated that many groups with higher risk for COVID-19 infection had lower willingness to take a COVID-19 vaccine. This finding is in accordance with pre-existing fault-lines of inequity in our society. Substantial vaccine uptake promotion is needed, and should be targeted to address inequities correlated with vaccine willingness.

Table 1. Likelihood of taking a COVID-19 vaccine in national probability serosurvey

| Characteristic                     | Very unlikely/somewhat unlikely/Unsure |            |            |        | Prevalence |           |
|------------------------------------|--|------------|------------|--------|------------|-----------|
|                                    | Survey n                               | Weighted n | Weighted % | 95% CI | Ratio*     | 95% CI    |
| Overall                            | 1,488                                  | 76,967,749 | 31.8       | 30-34% |            |           |
| Race/Ethnicity:                    |  |            |            |        |            |           |
| Hispanic                           | 202                                    | 12,002,153 | 29.8       | 24-36% | 0.98       | 0.79-1.22 |
| Non-Hispanic black                 | 367                                    | 12,447,149 | 45.6       | 37-54% | 1.50       | 1.22-1.85 |
| Non-Hispanic white                 | 836                                    | 46,453,862 | 30.3       | 28-33% | reference  |           |
| Other                              | 83                                     | 6,064,585  | 28.8       | 22-37% | 0.95       | 0.71-1.27 |
| Employment:                        |  |            |            |        |            |           |
| Working from home                  | 204                                    | 7,832,297  | 21.2       | 17-26% | reference  |           |
| Working outside the home           | 683                                    | 40,032,646 | 37.9       | 34-42% | 1.79       | 1.42-2.26 |
| Smoking:                           |  |            |            |        |            |           |
| No                                 | 1,140                                  | 55,020,480 | 28.8       | 26-31% | reference  |           |
| Yes                                | 319                                    | 20,491,874 | 43.6       | 38-50% | 1.51       | 1.29-1.78 |
| Serology:                          |  |            |            |        |            |           |
| Ig Negative                        | 1,386                                  | 71,219,333 | 31.1       | 29-34% | reference  |           |
| Ig Positive, diagnosed COVID-19    | 34                                     | 2,493,482  | 57.1       | 39-73% | 1.84       | 1.31-2.56 |
| Ig Positive, no diagnosed COVID-19 | 68                                     | 3,254,933  | 39.0       | 26-54% | 1.25       | 0.85-1.85 |

\*Prevalence ratio of responses very unlikely/somewhat unlikely/unsure versus responses very likely/likely

### 639 SARS-CoV-2 GENETIC DIVERSITY INCREASED AT LEAST 3-FOLD IN THE US IN 2020



**Adam A. Capoferri**<sup>1</sup>, Wei Shao<sup>2</sup>, Jonathan Spindler<sup>1</sup>, John M. Coffin<sup>3</sup>, Jason W. Rausch<sup>1</sup>, Mary F. Kearney<sup>1</sup>

<sup>1</sup>National Cancer Institute, Frederick, MD, USA, <sup>2</sup>Leidos Biomedical Research, Inc, Frederick, MD, USA, <sup>3</sup>Tufts University, Boston, MA, USA

**Background:** One year following the first detected SARS-CoV-2 (SC-2) infection in the U.S., there have been >26M cases and >440K deaths. During 2020, the virus spread in the U.S. in three phases: phase 1 (winter-spring), phase 2 (summer), and phase 3 (fall). We analyzed all publicly available SC-2 sequences from each phase to determine the effect of viral spread on its genetic diversity prior to the introduction of vaccines in mid-Dec 2020.

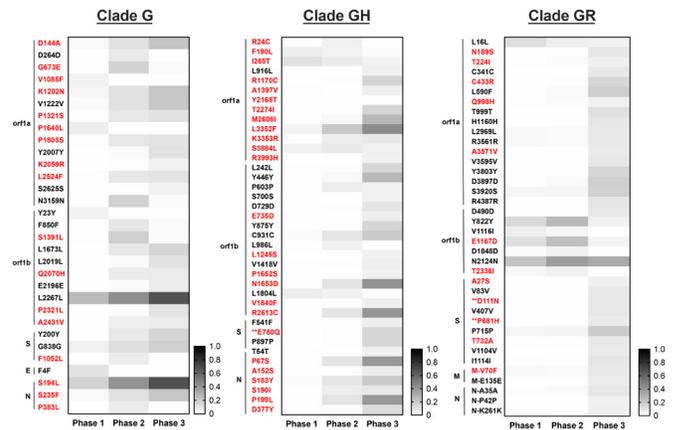
**Methods:** We obtained 36,299 U.S. SC-2 sequences from the GISAID submitted before Dec 15, 2020 (22,434 phase 1; 11,793 phase 2; and 2,072 phase 3).

Genetic diversity was measured for each clade in each phase by percent average pair-wise distance (%APD). Sequences were analyzed to detect new mutations present at frequencies exceeding 5% in each of the 3 phases.

**Results:** Six GISAID-defined clades (G/GH/GR/L/S/V) were each present in the U.S. by March 2020. The collective frequency of the three clades distinguished by the D614G mutation (G/GH/GR) increased from 83% in phase 1 to 99% in phases 2 & 3. Genetic diversity within these clades increased from 0.02% in phase 1 to 0.06% in phase 3. Non-synonymous (NS) mutations that emerged in clade G were in orf1a (7 mutations), orf1b (3), and N (3). Clade GH had the most NS mutations overall: orf1a (11), orf1b (5), S (1), and N (6), whereas Clade GR had the fewest but the most in the S gene: orf1a (6), orf1b (1), S (3), and M (1). Each of the detected mutations was unique to its respective clade. Full genome matches to variants from the U.K. (501Y.V1; clade GR) and South Africa (501Y.V2; GH) were not detected prior to Dec 15, possibly due to the delayed sequence submission to GISAID in the U.S. However, we did identify some individual S gene mutations matching those found in these variants. These mutations include 69-70del, 144del, and D1118H, and L18F, 242-244del, and E484K, respectively, each of which was already present at low frequency among sequences collected during phase 1.

**Conclusion:** Despite limited genomic sequencing in the U.S., we measured a 3-fold increase in SC-2 diversity in 2020 prior to the introduction of vaccines and identified at least 47 emerging amino acid changes. Three NS mutations in S were mapped to antibody epitopes and one (E484K) was previously shown to confer resistance to neutralizing antibodies. These findings underscore the critical importance of increased and timely genomic sequencing to ensure the future efficacy of SC-2 vaccines and treatments.

Figure 1 Heatmap of emerging mutations in G clades with frequencies exceeding 5%. Sequences were compared to the majority-consensus sequence for each respective clade in phase 1. Mutation designations reflect amino acid positions in products of the indicated genes. Red text denotes NS mutations. Mutations that occur in antibody epitope regions are denoted (\*\*). Gene abbreviations: S (Spike), E (Envelope), M (Matrix), and N (Nucleocapsid).



### 640



### PREVALENCE OF ANTI-SARS-CoV-2 ANTIBODIES IN SOUTH AFRICAN BLOOD DONORS

**Wendy Sykes**<sup>1</sup>, Russell Cable<sup>2</sup>, Charl Coleman<sup>1</sup>, Tanya Glatt<sup>1</sup>, Eduard Grebe<sup>3</sup>, Laurette Mhlanga<sup>4</sup>, Nadia Pieterse<sup>5</sup>, Ronel Swanevelder<sup>1</sup>, Karin van den Berg<sup>1</sup>, Marion Vermeulen<sup>1</sup>, Alex Welte<sup>1</sup>

<sup>1</sup>South African National Blood Service, Johannesburg, South Africa, <sup>2</sup>Western Cape Blood Service, Cape Town, South Africa, <sup>3</sup>Vitalant Research Institute, San Francisco, CA, USA, <sup>4</sup>South African Centre for Epidemiological Modelling and Analysis, Stellenbosch, South Africa, <sup>5</sup>Western Cape Provincial Department of Health, Cape Town, South Africa

**Background:** Given the inevitable, likely substantial, under-ascertainment of SARS-CoV-2 infection at the population level, using routine laboratory testing, the prevalence of SARS-CoV-2 antibodies ('seroprevalence') is an important marker of Covid-19 epidemiology. As nationally representative household surveys are a major undertaking, it will be important to find efficient ways to reliably estimate antibody prevalence from much simpler, less expensive protocols.

**Methods:** Subject to meeting standard blood donor eligibility criteria, and a standing opt-out arrangement for research use of specimens primarily obtained for blood safety screening, unsolicited blood donations, obtained on particular 'collection days' at 219 donation sites in South Africa, during January 2021, were tested for SARS-CoV-2 antibodies using the Roche Cobas e411 platform. Donors

are currently requested to defer donation if they were diagnosed with Covid-19, or experienced Covid-19-like symptoms, in the preceding 14 days. Estimates were stratified by age, sex and race. The study will have additional testing days. Phone interviews with both antibody positive and negative donors are being conducted to probe PCR diagnosis and symptoms.

**Results:** Tested donations numbered 4547, from donors aged 16-81.

Seroprevalence did not vary significantly between sexes or age groups. Headline results for the main race groups (in South African nomenclature) are: Black 58.3% (95% CI 55.8 – 60.7%), White 13.8% (95% CI 12.3 – 15.4%), Asian 23.4% (95% CI 19.4 – 27.7%) and Coloured 36.2% (95% CI 31.4 – 41.1%). The population group weighted overall national estimate is then 51.4% (95% CI 49.4 – 53.4%). This is almost 25 times as high as the official prevalence, on 10 January, of having been diagnosed with Covid-19, namely 2.1%. See Figure.

**Conclusion:** These are the first relatively widely representative SARS-CoV-2 antibody prevalence estimates from South Africa. Population level representativeness of this methodology warrants further exploration – but it is worth noting that 1) as elsewhere, the obtained antibody prevalence estimates imply SARS-CoV-2 attack rates that are easily an order of magnitude higher than the apparently relatively uninformative official case counts; and 2) the marginal cost of performing this study, over the cost of routine blood bank operations, was almost entirely comprised of the cost of reagents. South African case fatality rate estimates will need significant revision.

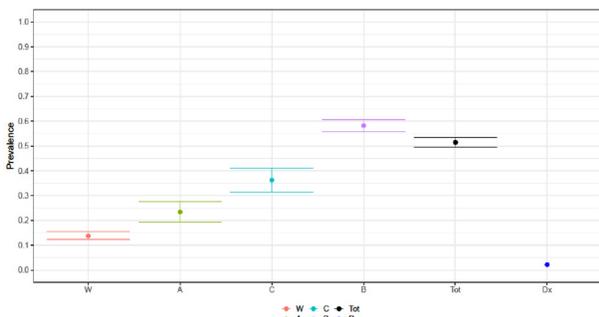


Figure: Estimated seroprevalence of anti-SARS-CoV-2 antibodies among South African blood donors in January 2021, by primary locally used racial designations (W)White, (A)Asian, (C)Coloured and (B)Black, as well as a race-weighted (Tot)al estimate and (Dx) the official prevalence of clinical Covid-19 diagnosis by PCR of nasal or oropharyngeal swab specimens.

#### 641 A PROSPECTIVE CASE-COHORT STUDY OF COVID-19 IN PERSONS WITH HIV: COV1H-19 STUDY



Jose L. Blanco<sup>1</sup>, Jose L. Casado<sup>2</sup>, José-Ramón Blanco<sup>3</sup>, Julián Olalla<sup>4</sup>, Elisa L. deLazzari<sup>1</sup>, Leire L. Berrocal<sup>1</sup>, Jesús Troya<sup>5</sup>, Hernando Knobel<sup>6</sup>, Jose Sanza-Moreno<sup>7</sup>, Angela Gutierrez<sup>8</sup>, Josep Cucurull<sup>9</sup>, Marta Navarro<sup>10</sup>, Arkaitz Imaz<sup>11</sup>, Esteban Martinez<sup>1</sup>, for the CoV1H-19 Spanish Group

<sup>1</sup>Hospital Clinic of Barcelona, Barcelona, Spain, <sup>2</sup>Hospital Ramón y Cajal, Madrid, Spain, <sup>3</sup>Hospital San Pedro, La Rioja, Spain, <sup>4</sup>Hospital Costa del Sol, Marbella, Spain,

<sup>5</sup>Hospital Universitario Infanta Leonor, Madrid, Spain, <sup>6</sup>Hospital del Mar, Barcelona, Spain, <sup>7</sup>Hospital Universitario Príncipe de Asturias, Madrid, Spain, <sup>8</sup>Hospital Universitario de La Princesa, Madrid, Spain, <sup>9</sup>Hospital de Figueras, Figueras, Spain,

<sup>10</sup>Hospital Universitario Parc Tauli, Sabadell, Spain, <sup>11</sup>Hospital Universitario de Bellvitge, Barcelona, Spain

**Background:** Several large cohort studies have shown that adults with HIV (PWH) may have worse COVID-19 outcomes than non-HIV-infected persons. Whether it may be due to a higher frequency of co-morbidities or to a direct HIV effect is currently unclear.

**Methods:** We performed a nation-wide multicenter prospective case-cohort study. Consecutive COVID-19-confirmed PWH (cases) admitted in 39 Spanish centers were matched 1:1 to COVID-19-confirmed non-HIV-infected adults (controls) for center, calendar week, age and gender. The contribution for death of HIV adjusted for co-morbidities was assessed in the whole population, and the contribution of immunological, virological, and antiretroviral factors only in the PWH group. Conditional logistic, random-effects logit and Fine-Gray competing-risks regression models were estimated.

**Results:** From 26/Feb to 21/Sep 2020, 204 cases and 204 controls were included. Median (IQR) age was 54 (47-60) years and 85% were men. Among PWH, 33% had prior AIDS events, current median CD4 cells/mm<sup>3</sup> were 521 (IQR 310-756), 14% had CD4 < 200/mm<sup>3</sup>, and 90% had HIV suppressed; antiretrovirals were: 17% NNRTI, 23% PI, 70% InSTI, 89% NRTI, 6% TDF, 45% TAF, and 31% ABC. Chronic liver disease (aOR 8.68, 95%CI 1.51-49.97, P=0.0156), cardiovascular

disease (aOR 2.09, 95%CI 1.19-3.68, P=0.0103), and obesity (aOR 0.30, 95%CI 0.19-0.49, P<0.0001) significantly differed between cases and controls. Twenty (9.8%) cases and 7 (3.4%) controls died. HIV infection was associated with a higher risk of death after adjustment for chronic liver disease, cardiovascular disease, and obesity (aOR 5.27, 95%CI 1.00-27.72, P=0.0499) and a higher incidence of death (subHR 3.45, 95%CI 1.47-8.11, P=0.0045). Increasing age, hypertension, diabetes, COPD, decreasing haemoglobin and leukocytes, and CKD-EPI eGFR ≤ 90 mL/min/1.73 m<sup>2</sup> were associated with death in cases, while increasing age and neoplasia were associated with death in controls. Only increasing age and COPD in cases and neoplasia in controls remained associated with death in the adjusted logistic regression. Current or nadir CD4 counts and CD4/CD8 ratio, detectable HIV RNA, and specific antiretroviral agents were not associated with death.

**Conclusion:** In this cohort of COVID-19 in-patients, risk of death was higher in PWH than in non-HIV-infected controls. Several co-morbidities through increasing age, but not immunological, virological, or antiretroviral factors, were associated with a higher risk of death in PWH.

642



#### DETERMINANTS OF COVID-19 HOSPITAL OUTCOMES IN A LARGE PENNSYLVANIA HEALTH SYSTEM

Pamela A. Shaw<sup>1</sup>, Jasper Yang<sup>1</sup>, Danielle L. Mowery<sup>1</sup>, Emily R. Schriver<sup>1</sup>, Kevin B. Mahoney<sup>1</sup>, Susan S. Ellenberg<sup>1</sup>, Katharine J. Bar<sup>1</sup>

<sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA

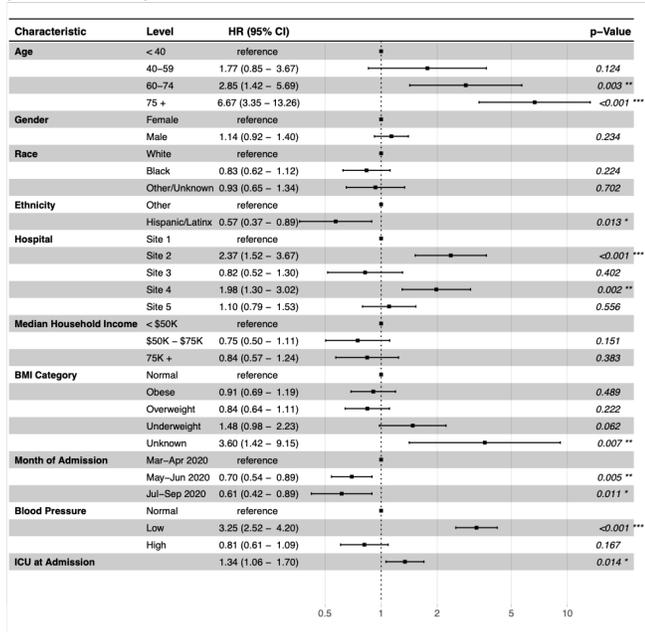
**Background:** Individuals hospitalized with COVID-19 exhibit a wide spectrum of disease. There is growing evidence that racial and ethnic minorities bear a disproportionate burden from COVID-19. Temporal changes in the pandemic epidemiology require careful study to identify determinants of poor outcomes. We assessed patient socio-demographics, comorbidities, baseline severity, treating hospital and pandemic month as independent risk factors for mortality and time to discharge.

**Methods:** We analyzed 2500 individuals hospitalized with PCR-confirmed COVID-19 in 5 hospitals in the University of Pennsylvania Health System between March and September 2020, using electronic health records to assess outcomes through 8 weeks post-admission. Hospital discharge and mortality were analyzed as competing risks using a multivariable cause-specific hazards model.

**Results:** Patients were 50.9% Black, 39.4% White and 9.7% other race; 11% were Hispanic. Mortality decreased markedly over time, with cumulative incidence (95% CI) 30 days post-admission of 19.1% (17.2, 21.3) in March-April versus 6.3% (4.3, 8.9) in July-September; 19% of deaths occurred after discharge. During this time, average age (SD) at admission declined from 62.7 (17.6) to 53.4 (20.6), ICU level care at admission increased from 16.5% to 18.6%, mechanical ventilation declined from 9.4% to 2.9%. Compared to Caucasian, Black race was associated with more severe disease at admission, a higher rate of co-morbidities and residence in low income zip code. In multivariable models, there were no detectable differences in mortality risk by race; while admitting hospital, increasing age, admission early in the pandemic, and severe disease and low blood pressure at admission were associated with increased mortality hazard (Figure 1). Mortality appeared similar between sexes, though males tended to have longer hospital stays (discharge hazard ratio 0.82 (95% CI: 0.75, 0.90)). Hispanic ethnicity was associated with fewer baseline co-morbidities and lower mortality hazard (0.57, 95% CI: 0.37, .087).

**Conclusion:** We found that morbidity and mortality for hospitalized COVID-19 patients substantially decreased over time but post-discharge mortality remained non-trivial. Black race was associated with more risk factors for morbidity and with treatment at hospitals with lower mortality. In multivariable models, there were no detectable race differences in hospital outcomes. Future work is needed to better understand the identified between-hospital differences in mortality.

**Figure 1: Mortality hazard ratios (HR) from the multivariate cause-specific Cox regression (model 1, n = 2493)<sup>1,2</sup>**



<sup>1</sup>7 observations deleted due to missingness in zip code (4) and blood pressure (3).  
<sup>2</sup>CI: Confidence interval; BMI: Body mass index. Site 1 (n=695), Site 2 (n=341), Site 3 (n=376), Site 4 (n=500), Site 5 (n=588) are unique hospitals in the University of Pennsylvania Health System.

Significant factors associated with spending 0-10% of follow-up time with viral load above 200 copies/ml (versus 11-100%) among people diagnosed with HIV in 2016 and 2017, District of Columbia

|   | Univariate           |         | Multivariate         |         |
|---|----------------------|---------|----------------------|---------|
|   | OR (95% CI)          | p-value | Adjusted OR (95% CI) | p-value |
| Age at HIV diagnosis (10-year increments) | 1.255 (1.078, 1.462) | 0.0034* | 1.223 (1.028, 1.455) | 0.0231* |
| Surveillance stage at HIV diagnosis       |                      |         |                      |         |
| Stage 1 (CD4 ≥ 500 cells/μl)              | Reference            | NA      | Reference            | NA      |
| Stage 2 (CD4 200-499)                     | 0.714 (0.457, 1.115) | 0.1382  | 0.810 (0.505, 1.299) | 0.3822  |
| Stage 3 (CD4 <200 cells/μl)               | 0.576 (0.308, 1.079) | 0.0852  | 0.515 (0.267, 0.992) | 0.0474* |

\* p < 0.05  
 Multivariable model covariates included gender, race, mode of HIV transmission, and residential ward.

**644 REFINING LATE HIV DIAGNOSIS ESTIMATES USING TESTING HISTORY AND IMMIGRATION DATA**

**Matthew R. Golden<sup>1</sup>, Susan Buskin<sup>2</sup>, Amy Bennett<sup>2</sup>, Julia C. Dombrowski<sup>1</sup>**  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Public Health—Seattle and King County, Seattle, WA, USA

**Background:** The percentage of HIV cases diagnosed late in infection is a metric for monitoring the adequacy of population-level HIV testing. CDC defines late diagnosis as a CD4 lymphocyte count <200 cells/ml or a clinical diagnosis of AIDS within 1 year of HIV diagnosis. The validity of this approach is uncertain.

**Methods:** We used surveillance data from persons diagnosed with HIV in King County, WA, USA 2010-2020 to compared 3 definitions of late diagnosis: 1) CD4 lymphocyte count <200 cells/ml or clinical AIDS diagnosis <1 year of HIV diagnosis; 2) definition 1 removing persons with acute HIV and those who report or had a documented HIV negative test in the 2 years prior to HIV diagnosis; and 3) definition 2 removing persons who reported a prior HIV diagnosis (unconfirmed per CDC criteria) or who were diagnosed within 1 year of immigrating to the US. We used published HIV natural history data to estimate the percentage of persons who would meet definition 1 assuming different distributions of time from infection to diagnosis.

**Results:** Among 2630 adults diagnosed with HIV 1652 had a defined date of last HIV negative test. CD4 count at time of HIV diagnosis was associated with time from last negative test (p<0.001, R<sup>2</sup>=0.039). However, 153 (13.1%) of 1161 persons with a negative test in the prior two years and 14 (6.2%) of 226 with acute HIV had AIDS within 1 year of HIV diagnosis, representing 23.1% of people identified as late diagnoses based on definition 1. Data on time since immigration were available for 496 (46.5%) of 1066 persons diagnosed with HIV born outside of the US. 375 persons with newly reported HIV infection – including 351 (32.9%) born outside of the US - reported an unconfirmed prior HIV diagnosis. The percentage of diagnoses classified as late for criteria 1, 2 and 3, were 25.9%, 19.9% and 16.8%, respectively. Incorporating additional data into late HIV diagnosis estimates decreased the number of late HIV diagnoses by one-third, with heterogeneous effects in different risk groups (Table). Modeling definition 1 using HIV natural history data, even if all persons with HIV tested within 2 years of infection, 6% would still be defined as late.

**Conclusion:** Estimates of late HIV diagnosis that depend on CD4 counts and AIDS diagnoses are likely too high in many settings. Integrating HIV testing history and information on nativity and immigration may improve estimates of late diagnosis.

Percentage of HIV Diagnoses Defined as Late Using Different Definitions of Late Diagnosis, King County, WA USA 2010-2020, by Risk Group

|  | Definition 1 | Definition 2 | Definition 3 | Overestimate of Late Infection (Definition 3 vs. 1) |
|--|--------------|--------------|--------------|---|
| All (n=2637)                                 | 25.9         | 19.9         | 16.8         | 35.1%   |
| MSM (including MSM/PWID) (n=1,826)           | 22.2         | 14.7         | 13.8         | 37.8%   |
| PWID (n=117)                                 | 27.3         | 23.9         | 23.1         | 15.4%   |
| Hetero (n=313)                               | 34.8         | 31.6         | 23.0         | 33.9%   |
| NRR (N=363)                                  | 37.2         | 35.2         | 25.1         | 32.5%   |
| African born persons (Hetero or NRR) (n=324) | 34.6         | 32.1         | 17.9         | 48.3%   |

MSM = Men who have sex with men; PWID = People who inject drugs; Hetero=Heterosexuals; NRR = No reported risk

**643 HIV VIRAL LOAD PATTERNS WITHIN 2 YEARS AFTER DIAGNOSIS IN WASHINGTON, DC**

**Rupali K. Doshi<sup>1</sup>, Alexandra Campione<sup>1</sup>, Kerri Dorsey<sup>1</sup>, Morgan Byrne<sup>1</sup>, Jenevieve Opoku<sup>2</sup>, Saanjh Boyani<sup>1</sup>, Anne Monroe<sup>1</sup>, Adam J. Visconti<sup>2</sup>, Michael Kharken<sup>2</sup>**  
<sup>1</sup>George Washington University, Washington, DC, USA, <sup>2</sup>District of Columbia Department of Health, Washington, DC, USA

**Background:** Sustained viral suppression (VS) following early treatment initiation among people diagnosed with HIV is key to reducing mortality, opportunistic infections, and transmission. We examined viral load (VL) patterns and associated demographics 2 years after diagnosis for the District of Columbia (DC).

**Methods:** Using DC's surveillance data, we included people diagnosed with HIV in 2016-2017 residing in DC at diagnosis, age ≥13 years at diagnosis, ≥2 VL tests after HIV diagnosis, and alive ≥2 years after diagnosis. We categorized VL patterns as Sustained VS (achievement and maintenance of VL <200 copies/ml for 2 years after diagnosis) or Unsustained VS (all others). We separately calculated the % time with VL above 200 copies/ml (TA200), categorized as 0-10% or 11-100%. Descriptive statistics including time from diagnosis to VS were assessed. We performed multivariable (MV) analyses to determine associations between demographic and clinical characteristics and sustained VS and 0-10% TA200.

**Results:** Of the 508 in the VL pattern analysis, 399 (79%) had Sustained VS and 109 (21%) had Unsustained VS. In the MV analysis, older age at diagnosis (aOR 1.24, 95% CI 1.01, 1.53; 10-year increments) and Ward 7 residence (aOR 2.92, 95% CI 1.02, 8.35) were associated with Sustained VS. Injection drug use as an HIV transmission risk factor was negatively associated with Sustained VS (aOR 0.20, 95% CI 0.07, 0.60). Of the 504 in the %TA200 analysis, 142 (28%) had 0-10% TA200 and 362 (72%) had 11-100% TA200. The median time from diagnosis to first viral suppression was 45 days (IQR 61) for the 0-10% TA200 group and 142 days (IQR182) for the 11-100% TA200 group. In the MV analysis, age at diagnosis (aOR 1.22, 95% CI 1.03, 1.46) and HIV stage (CD4 <200 cells/μl: aOR 0.52, 95% CI 0.27, 0.99) were associated with 0-10% TA200 (see Table).

**Conclusion:** Younger age, injection drug use, and stage 3 HIV were associated with worse VL patterns; people with these characteristics may need focused efforts to successfully enter HIV care. The findings can be used towards DC's efforts to End the HIV Epidemic by shortening the time from HIV diagnosis to ART initiation and VS. The absence of association with other demographic factors strongly suggests that factors not historically measured in surveillance should be examined to determine correlates of successful engagement in HIV treatment.

**645 THE EPIDEMIOLOGY OF ADVANCED HIV DISEASE BEFORE AND AFTER UNIVERSAL ART IN BOTSWANA**

**David S. Lawrence<sup>1</sup>**, Mark W. Tenforde<sup>2</sup>, Thandi Milton<sup>3</sup>, William Hurt<sup>3</sup>, Hannah Mitchell<sup>3</sup>, Kwana Lechiile<sup>4</sup>, Fredah Mulenga<sup>5</sup>, Charles Muthoga<sup>4</sup>, Christopher G. Williams<sup>4</sup>, Leah Owen<sup>3</sup>, Mooketsi Molefi<sup>6</sup>, Tshepo B. Leeme<sup>4</sup>, Julia Ngidi<sup>4</sup>, Madisa Mine<sup>5</sup>, Joseph N. Jarvis<sup>1</sup>  
<sup>1</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>2</sup>University of Washington, Seattle, WA, USA, <sup>3</sup>Botswana–University of Pennsylvania Partnership, Gaborone, Botswana, <sup>4</sup>Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, <sup>5</sup>Botswana National Health Laboratory, Gaborone, Botswana, <sup>6</sup>University of Botswana, Gaborone, Botswana

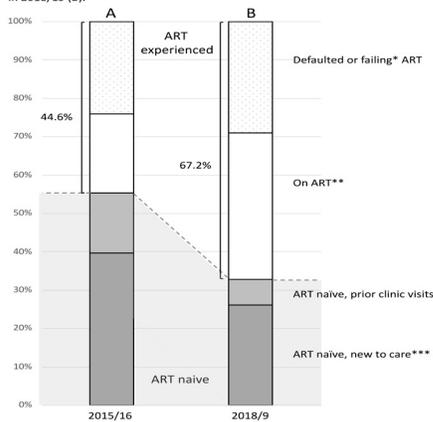
**Background:** The proportion of people living with HIV who have very advanced disease (CD4 < 100 cells/μL) has remained relatively constant over the past decade in sub-Saharan Africa, despite widened access to antiretroviral therapy (ART). We aimed to describe the characteristics of individuals presenting with very advanced HIV disease in Botswana before and after the introduction of universal ART and characterise the relationship between ART status and mortality.

**Methods:** We compared demographics and ART status in two cohorts of patients with CD4 counts < 100 cells/μL recruited into a reflex cryptococcal antigen (CrAg) screening program before (2015/16) and after (2018/19) the introduction of universal ART in Botswana. Data were collected from sequential individuals undergoing CD4 count assessment at the Botswana Harvard HIV Reference Laboratory in Gaborone. Associations between 6-month mortality and ART status were determined using a Cox regression analysis adjusted for age, sex, and CD4 count.

**Results:** 1645 individuals were included in the 2015/16 cohort and 743 in the 2018/19 cohort. Median age and sex were similar between cohorts (37 vs 39 years, 50% male vs 55% male); median CD4 counts were 54 cells/μL (IQR 25–78) and 59 cells/μL (IQR 31–83). The 2018/19 cohort were significantly more likely to be ART experienced, with 67% (499/743) either taking or having previously taken ART compared to 45% (734/1654) in the 2015/16 cohort (p < 0.001). In the 2018/19 cohort, 50 of 244 ART-naïve individuals had previously attended HIV care services, meaning only 26% (194/743) of individuals presenting with very advanced disease were new to care. In the combined cohorts, 6-month mortality was 10.4% (249/2388). Compared to those taking ART at presentation, 6-month mortality was higher in those who were ART naïve (HR 1.8, 95%CI 1.3–2.4) or who had defaulted ART (HR 1.6, 95%CI 1.0–2.4). Recent ART initiation (less than 3 months) was associated with increased mortality (HR 2.2, 95%CI 1.3–3.7).

**Conclusion:** The majority of patients in Botswana with very advanced HIV disease are now ART experienced and have previously been in HIV care. Mortality risk is highest among ART naïve individuals and those defaulting treatment, and declines rapidly once individuals are established on ART. These findings highlight the urgent need to identify individuals who have difficulty effectively engaging with HIV treatment services and improve their retention in care and adherence through differentiated service delivery models.

**Figure.** ART status of individuals presenting with very advanced HIV disease (CD4 count < 100 cells/μL) in Gaborone, Botswana, prior to universal treatment in 2015/16 (A) and following the introduction of universal antiretroviral therapy in 2018/19 (B).



The white shading shows ART experienced individuals, stratified into those either defaulting or failing ART\* (defined as a viral load of >400 copies/mL after at least 3 months on treatment) or those on ART\*\* for less than 3 months or more than 3 months with a suppressed viral load. The grey shading shows individuals who were ART naïve at the time of presentation with very advanced HIV disease, stratified into those who had documentation of prior HIV-related clinic visits more than 3 months prior presentation, and those who had no prior documented HIV-related clinic visits more than 3 months prior to presentation, and were classified as new to care\*\*\*.

**646 IMPACT OF AGING ON ART CONTINUATION FOR PERFORMANCE MANAGEMENT AND TARGET SETTING**

**Jessica Stephens<sup>1</sup>**, Lana Lee<sup>1</sup>, Noah Bartlett<sup>1</sup>, Melaku Dessie<sup>1</sup>, Mary Mahy<sup>2</sup>, George K. Siberry<sup>1</sup>

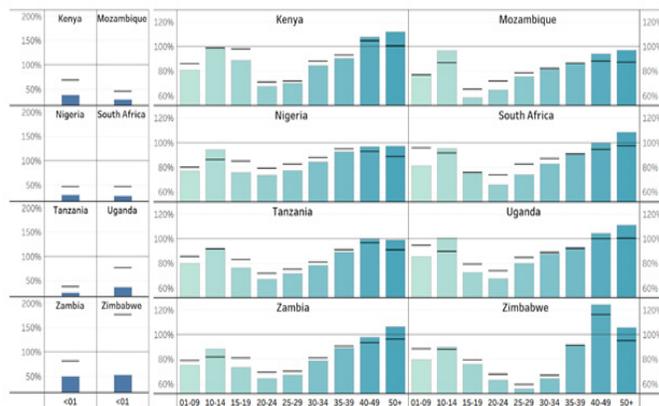
<sup>1</sup>United States Agency for International Development, Washington, DC, USA, <sup>2</sup>Joint United Nations Programme on HIV/AIDS, Geneva, Switzerland

**Background:** Retention of clients on HIV treatment is essential for achieving the second and third of the UNAIDS 90–90–90 goals. The President’s Emergency Plan for AIDS Relief (PEPFAR) requests programs to monitor age-specific retention using aggregated data, in order to identify demographic groups who may be experiencing treatment interruptions at higher rates. However, retention measures may be distorted by normal aging into and out of age bands. This analysis quantifies the impact of aging on PEPFAR retention estimates for eight PEPFAR priority countries: Kenya, Mozambique, Nigeria, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe.

**Methods:** We used data submitted to PEPFAR in 2018 and 2019 on people living with HIV (PLHIV) currently receiving antiretroviral therapy (ART) (TX\_CURR), PLHIV newly enrolled on ART (TX\_NEW), and UNAIDS Spectrum Modeling for the number of PLHIV on ART by one-year age band. We calculated proxy retention as currently calculated by PEPFAR [TX\_CURR 2019 / (TX\_CURR 2018 + TX\_NEW 2019)] and compared it to the proxy retention but adjusted for aging (“aging adjusted PEPFAR retention” [AAPR]) [TX\_CURR 2019 / (aging-adjusted TX\_CURR 2018 + TX\_NEW 2019)]. To calculate the aging-adjusted TX\_CURR 2018, first we predicted baseline ART in 2019 using Spectrum estimates for 2018. Next, we aggregated predicted baseline 2019 and 2018 in 2018 age band groups (<1, 1–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–49, 50+). Finally, we took the proportion of predicted baseline 2019 relative to 2018, which we applied to the TX\_CURR 2018.

**Results:** After adjusting for aging, estimates of retention on ART increases for most age bands compared to the current PEPFAR retention proxy approach, except for 10–14 and >40. Adjusted for aging, proxy retention on average increased for <1 by 37.2% (AAPR: 73.8%); 1–9 by 3.3% (AAPR: 83.0%); 15–19 by 6.8% (AAPR: 81.5%); 20–24 by 6.0% (AAPR: 72.8%); 25–29 by 4.6% (AAPR: 76.1%); 30–34 by 3.1% (AAPR: 83.6%); and 35–39 by 1.2% (AAPR: 91.8%). Proxy retention adjusted for aging on average decreased for 10–14 by 2.8% (AAPR: 91.7%); 40–49 by -4.5% (AAPR: 98.7%) and 50+ by 10.0% (AAPR: 94.8%).

**Conclusion:** Normal aging can distort age-band retention estimates, especially at the extremes of ages. Assessment of retention for <1 age band needs special treatment, as all infants will age out over the course of one year. Treatment programs need systematic methods to account for aging to better assess and optimize continuity of care across the lifespan.



**647 PATIENT TRANSFERS BETWEEN PRIMARY CARE ART SERVICES IN THE WESTERN CAPE, SOUTH AFRICA**

**Jasanthia Odayar<sup>1</sup>**, Benjamin Chi<sup>2</sup>, Tamsin K. Phillips<sup>1</sup>, Elton Mukonda<sup>1</sup>, Marvin Hsiao<sup>1</sup>, Maia Lesosky<sup>1</sup>, Landon Myer<sup>1</sup>

<sup>1</sup>University of Cape Town, Cape Town, South Africa, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

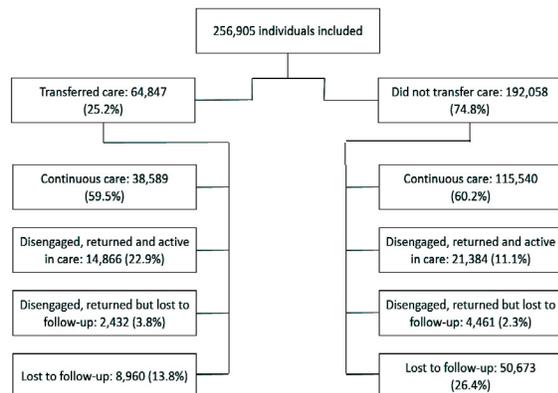
**Background:** People living with HIV (PLH) on antiretroviral therapy (ART) require longitudinal care, frequently delivered across multiple health facilities. However there are few data on how transfers of PLH between primary health care (PHC) facilities could affect ART adherence and retention.

**Methods:** We constructed a cohort of all patients on ART in the Western Cape province (2008-2018) using viral load (VL) data from the National Health Laboratory Service. VL testing is routinely available and recommended at 6m after ART start and then yearly. Unique patient identifiers and probabilistic matching linked individuals across facilities; PLH >16y with >2 VLs in the study period (>1 VL at a PHC facility) were included; new patients were censored after 2016 to allow >2y follow-up. Transfers were defined as PLH with VLs recorded at >1 PHC facility. Transfer-out (TFO) was recorded as the last VL date at the original facility. Loss to follow-up at analysis closure (LTFU, no VL in the last two years of follow-up), disengagement with return to care (RTC, >2y between consecutive VLs), and VL>50 cps/mL were compared in those who did and did not TFO. We also described subsequent viremia (VL>50 cps/mL) among those with VL<50 cps/mL at TFO.

**Results:** Overall, 256,905 PLH were included in the analysis (69% female, median age 34y [IQR 28-40], median follow-up 4y [IQR 2-6]); 64,847 (25%) had >1 TFO between PHCs (Figure). Time from ART initiation to TFO was 13m (IQR 6-34) and 27% had a VL>50 cps/mL at TFO. Increased TFO rates were observed with: age <30y (adjusted rate ratio [aRR]; 95%CI: 1.31; 1.29-1.33), female sex (1.25; 1.23-1.27), first VL in a rural district (1.26; 1.24-1.29) and first VL>50 cps/mL (1.06; 1.05-1.08). Compared to PLH who did not TFO, PLH who TFO were more likely to have >1 episode of disengagement with RTC (27% vs 14%; aRR 1.95; 1.91-1.99) and were less likely to be LTFU at the end of observation (18% vs 29%; aRR 0.62; 0.60-0.63). Among 183,151 PLH whose first VL was <50 cps/mL, those who TFO were more likely to develop a VL>50 cps/mL versus those who did not (43% vs. 34%, p<0.05). In 47,134 patients with VL<50 cps/mL at the time of TFO, 34% developed a VL>50 cps/mL at a median 31m (IQR 18-48) after transfer.

**Conclusion:** Transfer between PHC occurs frequently and PLH who transfer may be vulnerable to disengagement from care and viremia, pointing to the need for intervention strategies to support the transfer process.

Figure: Engagement in care in patients on ART who do and do not transfer between PHC facilities



## 648 PREDICTING RISK OF HIV ACQUISITION IN RURAL SOUTH AFRICA USING GEOGRAPHIC DATA

Allen Roberts<sup>1</sup>, Diego Cuadros<sup>2</sup>, Alain Vandormael<sup>3</sup>, Dickman Garetta<sup>4</sup>, Ruanne Barnabas<sup>1</sup>, Kobus Herbst<sup>4</sup>, Frank Tanser<sup>5</sup>, Adam Akullian<sup>6</sup>

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>3</sup>Heidelberg University, Heidelberg, Germany, <sup>4</sup>Africa Health Research Institute, Mtubatuba, South Africa, <sup>5</sup>University of Lincoln, Lincoln, United Kingdom, <sup>6</sup>Institute for Disease Modeling, Bellevue, WA, USA

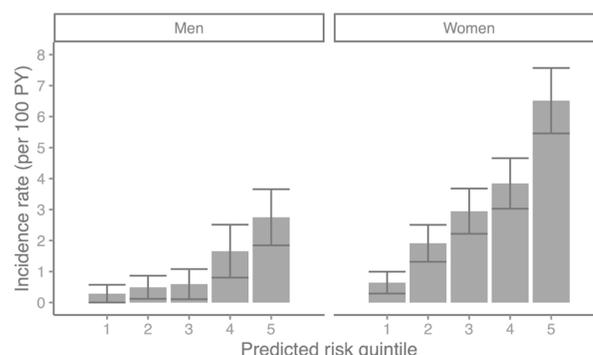
**Background:** Accurate HIV risk assessment is needed to optimize resource allocation for HIV prevention. Existing risk scoring tools are primarily based on individual-level measures such as age and sexual behavior. Community HIV prevalence and viral load are proxies for HIV transmission potential and could inform risk prediction.

**Methods:** We developed and validated gender-specific HIV risk prediction models using data from the Africa Health Research Institute's population-based cohort in rural KwaZulu-Natal, South Africa. Eligible individuals were aged 15-54 years with an HIV-negative test and at least one subsequent HIV test. Individual covariates included demographic, socioeconomic, and sexual behavior measures collected via annual household surveys. Geospatial covariates included annual small area estimates of HIV prevalence and viral load constructed from home-

based surveillance. Geospatial surfaces were estimated using a 3 km bandwidth Gaussian kernel, and covariate values were assigned to each individual based on their location of residence. We trained models on data from 2012 to 2015 using Cox proportional hazards regression models with time-varying covariates and with lasso penalties selected via cross-validation. We validated model predictions on data from 2016 to 2019 and assessed performance using area under the ROC curve (AUC). We compared full models (based on both individual and geospatial covariates) to models trained only using age and geospatial covariates.

**Results:** The training and validation cohorts combined included 19,556 individuals contributing 44,871 person-years (PY) at risk and 1,308 seroconversions. The full models had AUCs of 0.68 among women and 0.72 among men in validation. Incidence in the validation cohort among the highest predicted risk quintile was 6.58/100 PY among women and 2.84/100 PY among men; these quintiles accounted for 39% and 47% of new infections in women and men, respectively. Models using only age group and geospatial covariates had AUCs of 0.65 for women and 0.71 for men in validation.

**Conclusion:** Our risk prediction models identified individuals at high risk for HIV acquisition who could benefit from prevention interventions like PrEP. A geospatial model with no individual measures other than age group performed nearly as well as the full model. Geographic risk prediction models may help prioritize interventions to specific individuals and geographic areas at highest risk without the need to collect individual-level behavioral data.



## 649 GEOSPATIAL RISK PROFILES PREDICT INCIDENT-HIV AREAS IN HYPERENDEMIC AFRICAN NATION

Neena M. Philip<sup>1</sup>, Gina S. Lovasi<sup>2</sup>, Rejoice Nkambule<sup>3</sup>, Frank Tanser<sup>4</sup>, Quarraisha Abdool Karim<sup>5</sup>, Jessica Justman<sup>1</sup>, Barun Mathema<sup>6</sup>

<sup>1</sup>ICAP at Columbia University, New York, NY, USA, <sup>2</sup>Drexel University, Philadelphia, PA, USA, <sup>3</sup>Ministry of Health, Mbabane, Swaziland, <sup>4</sup>University of Lincoln, Lincoln, UK, <sup>5</sup>Centre for the AIDS Programme of Research in South Africa, Durban, South Africa, <sup>6</sup>Columbia University, New York, NY, USA

**Background:** The cause of the geographic variation in HIV epidemics across generalized hyperendemic settings is poorly understood. We assessed the role of geospatial clustering of HIV risk factors including viral load within nationally representative census enumeration areas (EAs) to predict prospectively observed incident infections in the hyperendemic setting of Eswatini.

**Methods:** In 2011, a household-based sample of 18,172 adults, ages 18-49 years, from 575 EAs received HIV testing and completed an administered questionnaire. All HIV-seropositive samples were tested for HIV RNA. HIV-seronegative adults were retested and reinterviewed six months later. Multi-level latent class modeling was used to identify statistically significant combinations of seven HIV risk factors (i.e., sexual activity, number of partners, casual partnerships, partner HIV status, condom use, HIV viremia at  $\geq 20$  copies/milliliter among all adults regardless of HIV status, and gender-age group) and to classify them into EA risk profiles of composite EA prevalences of HIV risk factors. Generalized linear regression was used to assess whether EA-level HIV seroconversion (i.e. if an EA had at least one HIV seroconversion during the follow-up period) was associated with EA risk profiles or with the observed mean EA prevalence of any single HIV risk factor across all 575 EAs.

**Results:** Of 11,880 HIV uninfected adults (51% male, 45% 18-24 years), 11,155 (94%) completed follow-up. Based on all risk factors, four EA risk profiles were identified, ranging from lowest (Profile A) to highest (Profile D) risk of new infections. Prevalence of EA-level HIV seroconversion increased across profiles: A (14.3%), B (21.8%), C (24.6%) and D (30.8%). EA-level HIV seroconversion

was twofold higher in Profile D than Profile A areas [relative risk 2.13, 95% confidence interval (1.13, 4.00),  $p=0.02$ ]. The prevalences of unknown partner HIV status and detectable viremia in Profile D were 28% and 24%, respectively, compared to 8% and 31% in Profile A. In isolation, none of the observed mean EA prevalences of any risk factor was independently associated with EA-level HIV seroconversion.

**Conclusion:** In a generalized epidemic, a composite geospatial measure of concurrent HIV risk factors including viremia was better than viremia alone in predicting HIV incidence at an EA level. Tailoring HIV prevention and treatment interventions to area patterns of HIV risk factors may optimize the impact of national HIV response efforts in similar settings.

Area profiles of clustered HIV risk factors and the association with area-level HIV seroconversion

| Profile prevalence (%)                                  | Area risk profile* (N=575) |                  |                  |                  |
|---|----------------------------|------------------|------------------|------------------|
|   | A                          | B                | C                | D                |
| Profile prevalence (%)                                  | 15                         | 56               | 17               | 12               |
| Profile-specific area prevalence of HIV risk factor (%) |                            |                  |                  |                  |
| Sexual activity   | 94                         | 84               | 91               | 85               |
| Two or more partners                                    | 10                         | 8                | 17               | 9                |
| Casual partner  | 5                          | 6                | 17               | 9                |
| Partner with unknown HIV status                         | 8                          | 8                | 13               | 28               |
| Never use a condom                                      | 42                         | 39               | 28               | 33               |
| HIV viremia† (≥20 copies/mL)                            | 31                         | 21               | 27               | 24               |
| Relative risk of area-level HIV seroconversion          | ref                        | 1.51 (0.88-2.65) | 1.55 (0.83-2.87) | 2.13 (1.13-4.00) |

\* Describes the four most common combinations of risk factors among enumeration area populations. Each profile is a composite prevalence of risk factors during the follow-up period, among a subset of similar enumeration area-specific HIV-seronegative populations. † HIV viremia was measured at baseline and includes all 18,172 adults, regardless of HIV status.

**650 SEXUAL-AFFILIATION-NETWORK ANALYSIS TO INFORM VENUE-BASED HIV INTERVENTIONS IN PERU**

Alexander Lankowski<sup>1</sup>, Jose Hidalgo<sup>2</sup>, Robinson Cabello<sup>2</sup>, Hugo Sanchez<sup>3</sup>, Ann C. Duerr<sup>4</sup>

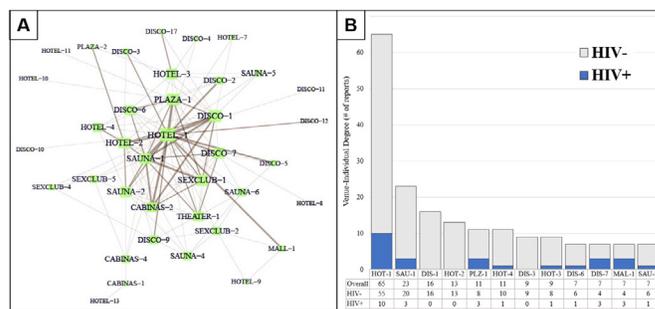
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Via Libre, Lima, Peru, <sup>3</sup>Epicentro, Lima, Peru, <sup>4</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA

**Background:** To curb the ongoing high HIV incidence in men who have sex with men (MSM) and transgender women (TW) in Peru, HIV control interventions would benefit from improved targeting of those at highest risk. Analysis of "sexual affiliation networks", comprised of individuals and the venues where they meet sex partners, is an indirect and information-rich approach that could inform such efforts by identifying "high-risk" venues for outreach. We hypothesized that sexual affiliation network analysis would reveal a subset of venues in Lima, Peru where MSM and TW in high-risk sexual networks could be contacted for HIV testing and linkage to services.

**Methods:** We recruited adult MSM and TW presenting for voluntary HIV testing at Via Libre, a large HIV clinic in downtown Lima, to complete a brief survey asking about the physical venues where they met a sex partner in the last 3 months. We also collected data on sexual risk behaviors and HIV test result. Using the igraph package in R, we first reconstructed the venue-individual (2-mode) affiliation network comprised of venues reported by ≥2 MSM/TW and the MSM/TW who reported them. To evaluate venue connectivity, network prominence, and relationship to HIV transmission risk (based on HIV positivity rate of participants), we then analyzed the venue-venue (1-mode) co-affiliation network comprised of venues named by ≥2 MSM/TW.

**Results:** Of 344 (52%) total survey participants, 178 reported ≥1 sex partner meeting venue (analysis population): 155 (87%) were MSM and 23 (13%) TW; median age was 26 (interquartile range [IQR], 22 – 32); and 28 (16%) tested positive for HIV on the day of the study. Overall, 44 unique venues were included in the network analysis: 14 hotels, 12 discos, 5 saunas, 4 internet "cabins", 4 sex clubs, 2 plazas, 2 malls, and 1 theater). Visualization of the venue-venue co-affiliation network (Panel A) in conjunction with ordered ranking of network centrality (superimposed with venue-level HIV positivity) (Panel B) identifies a densely connected subset of venues (e.g. Hotel-1, Sauna-1, Plaza-1) with high venue-level HIV positivity.

**Conclusion:** Sexual affiliation network analysis revealed a core subset of highly connected venues in Lima that may be ideal sites at which to reach MSM/TW in high-risk sexual networks. Our results highlight a potentially valuable role for sexual affiliation network analysis as a tool to aid public health systems in effectively targeting HIV testing and prevention interventions to interrupt HIV transmission.



**Panel A:** Co-affiliation network of physical venues in Lima where ≥2 participants (n=178 MSM/TW) reported meeting a recent sex partner (n=38 venues included after removing isolates [i.e. venues not connected to any other venue in network]) in Lima, Peru, February 2019 – March 2020. Venues are linked if they have at least one shared individual. Weight of the line connecting two venues reflects the number of shared individuals (i.e. wider line indicates more MSM/TW reported both venues). Node and label font size reflects level of venue-venue degree centrality (i.e. larger node/label indicates more venue connections).

**Panel B:** Ordered ranking of venues by venue-individual degree centrality (i.e. # of reports) across an affiliation network of sex partner meeting venues reported by ≥2 MSM/TW in Lima, Peru (graph limited to subset of 12 most reported venues). Overall bar height corresponds to the # of MSM/TW reporting a given venue as a sex partner meeting place (i.e. venue-individual degree centrality), with blue bars indicating the number of those who were identified as HIV+ (previously undiagnosed) based on test done at time of study participation. HOT = Hotel, SAU = Sauna, DIS = Bar/Disco, PLZ = Plaza, MAL = Mall.

**651 PHYLOGENETICS REVEAL SHIFTING PATTERNS IN HIV-1 SPREAD IN QUEBEC FROM 2002 TO 2019**

Bluma G. Brenner<sup>1</sup>, Ruxandra-Ilinca Ibanescu<sup>2</sup>, Jean-Pierre Routy<sup>3</sup>, Réjean Thomas<sup>4</sup>, Cécile Tremblay<sup>5</sup>, Nadine Kronfli<sup>6</sup>, Bertrand Lebouche<sup>3</sup>, Nathan Osman<sup>1</sup>, Isabelle Hardy<sup>6</sup>, Jean-Guy Baril<sup>6</sup>, Joanne Otis<sup>7</sup>, Michel Roger<sup>5</sup>, for the Montreal Primary HIV Infection Cohort

<sup>1</sup>Lady Davis Institute for Medical Research, Montreal, Canada, <sup>2</sup>Lady Davis Institute, Montreal, Canada, <sup>3</sup>Research Institute of McGill University Health Centre, Montreal, Canada, <sup>4</sup>Clinique Médicale l'Actuel, Montreal, Canada, <sup>5</sup>Centre de Recherche du CHUM, Montreal, Canada, <sup>6</sup>Centre Hospitalier de l'Université de Montréal, Montreal, Canada, <sup>7</sup>Montreal Clinical Research Institute, Montreal, Canada

**Background:** Phylogenetic analyses of the interrelationships of viral sequences from the Quebec genotyping program have provided a molecular epidemiological framework to reconstruct HIV transmission networks in Quebec. We applied these methods to elucidate transmission dynamics and epidemic drivers fueling HIV spread among Men having Sex with Men (MSM) and Heterosexual groups.

**Methods:** Phylogenetic analyses on HIV-1 polymerase sequences was performed using Maximum Likelihood methods and HIV-TRACE (Transmission Cluster Engine) platforms. Transmission clustering was ascertained based on high bootstrap support and genetic distance (<1.5%). Time trends in viral spread and clustering was assessed in i) MSM, (male singletons and clusters, n=6996); ii) Heterosexuals harboring subtype B infections including recent migrants from the Caribbean and the Americas (n=1902); and iii) Heterosexuals harboring non-B viral subtypes (n=1549). Cluster membership and size was related to viral load, disease stage, treatment status, and viral sequence recency (based on % mixed base calls).

**Results:** HIV-1 transmission dynamics among MSM was stratified into three groups based on phylogenetic clustering: singleton transmissions (n=1404), small cluster networks (2-5 members/cluster, n=884) and large cluster micro-epidemics (6+ members/cluster n=2371, median 31 members/cluster). 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 (Spearman  $r = -0.295$  and  $-0.235$ ,  $p < 0.001$ ). Annual numbers of new HIV-1 infections have steadily declined among MSM post-2008, concomitant to improved treatment-as-prevention paradigms and declines in community viral load. The declines in singleton transmissions over the 2014-2019 period as compared to the 2002-2007 and 2008-2013 periods reflected declines in chronic stage transmissions. Heatmaps show how epidemic control among MSM has been offset by the ongoing genesis and expansion of large cluster outbreaks. Recent arrivals to Quebec accounted for a growing number of subtype B and non-B subtype infections. Phylogenetics reveal shifting patterns of HIV spread among MSM and HET groups.

**Conclusion:** HIV-1 epidemic control will require improved testing and prevention paradigms to avert late diagnosis leading to transmission cascades in younger persons and new arrivals to the province.

## 652 DYNAMICS OF HIV TRANSMISSION BETWEEN HIGH-RISK POPULATIONS IN TIJUANA

Heather A. Pines<sup>1</sup>, Sanjay R. Mehta<sup>1</sup>, Daniela Abramovitz<sup>1</sup>, Alicia Harvey-Vera<sup>1</sup>, Thomas L. Patterson<sup>1</sup>, Claudia Rafful<sup>2</sup>, Gudelia Rangel<sup>3</sup>, Steffanie Strathdee<sup>1</sup>, Antoine Chaillon<sup>1</sup>

<sup>1</sup>University of California San Diego, San Diego, CA, USA, <sup>2</sup>National Autonomous University, Mexico City, Mexico, <sup>3</sup>Comisión de Salud Fronteriza/Colegio de la Frontera Norte, Mexico City, Mexico

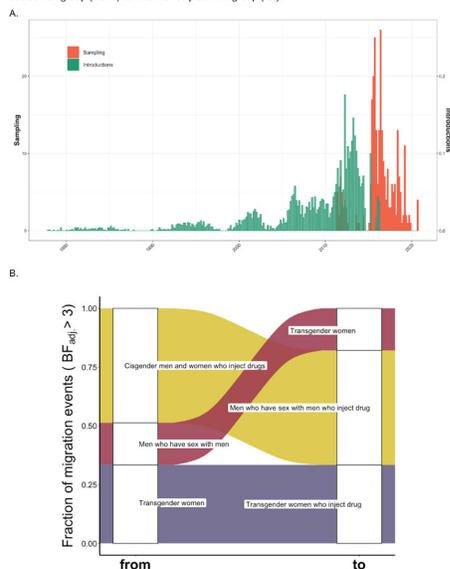
**Background:** Tijuana, Mexico is situated on the Mexico-US border and home to many individuals at high HIV risk. We characterized the dynamics of HIV transmission between high-risk populations in Tijuana to inform the development of targeted interventions in this binational context.

**Methods:** Using a comprehensive data set of HIV-1 B partial pol sequences sampled in Tijuana between 2011 and 2020 from (1) Proyecto Enlaces (PE, N=232 men who have sex with men or transgender women (MSM or TGW) and TGW living with HIV; N=187 with HIV-1 pol data) and (2) Proyecto El Cuete (ECIV, N=942 cisgender women [CW] and cisgender men [CM] who report injection drug use [IDU]; N=68 with HIV-1 pol data), we applied the following multistep phylogenetic approach: (1) maximum likelihood phylogenetic inference to identify well-supported monophyletic clades from PE/ECIV (i.e., putative transmission clusters); (2) all clades identified in step 1 were used to perform a discrete phylogeographic inference to evaluate historical introductions of HIV into Tijuana and transmission dynamics between risk groups defined based on participants' IDU in the past month, gender identity, and the gender identity of their recent sex partners (i.e., CW and CM; MSM and TGW who did and did not report IDU).

**Results:** Our analysis (N=255) included sequences from 166 (65.1%) MSM, 21 (8.2%) TGW, 37 (14.5%) CM, and 31 (12.2%) CW, with 87 (33.6%) and 93 (35.9%) reporting recent IDU and transactional sex, respectively. After combining these with 107,953 publicly available HIV-1 pol sequences, we identified 15 supported clades of size  $\geq 3$  (N=88 sequences) and 39 introductions into the local epidemic (most recent common ancestor=2008.6 [95%: 1987.6-2015.9], Fig.1A). Discrete phylogeographic analysis of the identified clades revealed high levels of transmission events from CW and CM reporting IDU toward MSM reporting IDU (50% of all supported transmission events), between TGW who did and did not report recent IDU (30%), and from MSM toward TGW both of whom did not report recent IDU (20%) (Fig.1B). Overall, 32% of transmission events originated from people who reported transactional sex.

**Conclusion:** Our findings suggest an important role of IDU in the bridging of HIV transmission across high-risk populations in Tijuana. Efforts to decrease HIV transmission among those reporting IDU and sex work may confer HIV prevention benefits across high-risk populations in Tijuana and the broader Mexico-US border region.

**Figure 1. A. Number of introduction events toward Tijuana.** The number of introduction events within Tijuana using Proyecto Enlaces, Proyecto El Cuete, and all publicly available HIV-1 B sequences with known location (n=107,953) is depicted in green. The sampling density (i.e., number of sequences included in the model) is presented in red. **B. Relative contribution of risk groups to the spread of HIV in Tijuana.** Results based on the clade-identification using Shimodaira Hasegawa (SH) branch support  $\geq 0.9$  and accounting for migration links associated with an adjusted Bayes factor (BF<sub>adj</sub>)  $\geq 3$ . The Sankey plot represents the proportion of migration events from each source risk group ("from") toward the recipient risk group ("to").



## 653 HIV MOLECULAR TRANSMISSION NETWORKS SENSITIVITY TO DATA COMPLETENESS

Sepideh Mazrouee<sup>1</sup>, Ricardo Mora<sup>2</sup>, Rocío Carrasco-Hernandez<sup>1</sup>, Michelle Carr<sup>2</sup>, Natascha Del Vecchio<sup>3</sup>, Kayo Fujimoto<sup>4</sup>, Marlene McNeese<sup>2</sup>, Camden J. Hallmark<sup>2</sup>, Joel Wertheim<sup>1</sup>

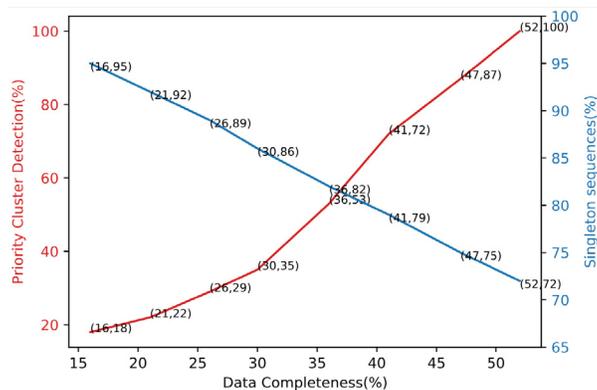
<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>Houston Health Department, Houston, TX, USA, <sup>3</sup>University of Chicago, Chicago, IL, USA, <sup>4</sup>University of Texas at Houston, Houston, TX, USA

**Background:** Accurate detection of viral molecular transmission clusters is critical to the respond pillar of the Ending the HIV Epidemic initiative, which aims to reduce HIV transmission by 90% in ten years. Previous analysis with high data completeness has shown that artificially lowering molecular surveillance completeness can preclude cluster detection and tracking of HIV outbreaks. Here, we investigate whether lack of access to the entire dataset of all people living with HIV would influence the accuracy of reconstructed molecular transmission networks and consequently lower effectiveness of public health interventions.

**Methods:** We analyzed viral genomic data of 12,818 individuals with diagnosed HIV (2012-2019) from Houston Health Department surveillance data with 52% completeness. We used HIV-TRACE to reconstruct a transmission network using first reported pol sequence and identified priority clusters based on the CDC-specified criteria. To understand the impact of lower-completeness, we performed 10-fold random subsampling by removing records (in 10% decrements) without replacement. Next, we subsampled based on node influence. Expected Force (ExF) computes spreading power of individual nodes via adopting a relative influence of different walk and walk lengths based on local connectivity in a network. We computed ExF for each node in the network. Then we removed nodes with highest or lowest ExF from the full dataset. We reconstructed the network twice (0.5% & 1.5% genetic distance) for all completeness levels to measure the impacts for the above subsamples.

**Results:** Randomly subsampled data, the detection rate of priority clusters decreased in low completeness (Figure 1). We also observed that the number of singletons expanded up to 95% of all sequences with lower completeness. Next, we compared detection of priority clusters in networks where we filtered out all high ExF (influence) nodes and only 4.7% of priority clusters were detected in comparison with full data. We repeated the experiment with removal of lowest ExF nodes, yet 60% of priority clusters were detected with nearly a quarter of sequences which is far greater than random subsampling detection.

**Conclusion:** Our results indicate that exhaustively expanding molecular surveillance data to 100% sequence data completeness will have diminishing returns on identification of priority clusters. Network metrics like node influence should be considered to optimize cluster detection.



**654 TRENDS AND DISPARITIES IN ACHIEVING VIRAL SUPPRESSION IN THE UNITED STATES, 2012-2018**

**Elizabeth Humes<sup>1</sup>**, Jennifer Lee<sup>1</sup>, Jun Li<sup>2</sup>, David B. Hanna<sup>3</sup>, Vincent Marconi<sup>4</sup>, Jonathan Colasanti<sup>5</sup>, Heidi Crane<sup>6</sup>, Mari M. Kitahata<sup>6</sup>, Ronald J. Bosch<sup>7</sup>, Sarita Shah<sup>4</sup>, Michael J. Silverberg<sup>8</sup>, Keri N. Althoff<sup>1</sup>, Richard Moore<sup>9</sup>, Kate Buchacz<sup>2</sup>, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

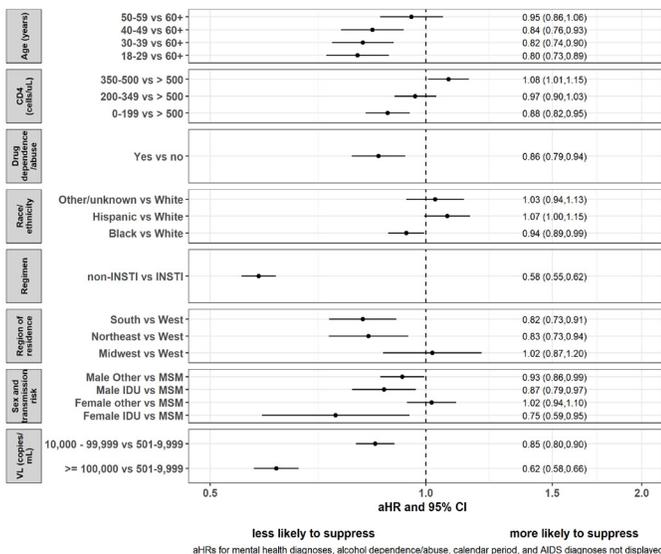
<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>3</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>4</sup>Emory University, Atlanta, GA, USA, <sup>5</sup>Emory University School of Medicine, Atlanta, GA, USA, <sup>6</sup>University of Washington, Seattle, WA, USA, <sup>7</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>8</sup>Kaiser Permanente, Oakland, CA, USA, <sup>9</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Treating people with HIV (PWH) rapidly and effectively to achieve viral suppression (VS) is a key strategy in the US for the Ending the HIV Epidemic (EHE) Initiative. VS is critical for PWH to achieve optimal health outcomes and reduce the likelihood of drug resistance and further HIV transmission. We assessed initial VS 6 months after antiretroviral therapy (ART) initiation and characterized PWH who did not achieve this outcome.

**Methods:** We analyzed data on ART-naïve PWH ≥18 years of age who newly presented to care and initiated ART between 1/1/2012-6/30/2018 from 13 NA-ACCORD clinical cohorts. PWH with a clinical AIDS diagnosis > 30 days prior to care entry or viral load (VL) ≤500 copies/mL prior to care entry were excluded. Patients were followed from ART initiation until initial VS (1 VL <200 copies/mL), death, loss to follow-up, or 6 months after ART initiation. The cumulative incidence of initial VS 6 months after ART initiation was calculated using the Kaplan–Meier estimator and stratified by calendar year. Adjusted hazard ratios (aHR) for initial VS 6 months after ART initiation were calculated using discrete time-to-event models that included the following variables at ART initiation: age, sex and HIV acquisition group, race/ethnicity, CD4 count and VL, mental health diagnoses, alcohol or drug dependence/abuse, geographic region of residence, AIDS diagnosis, ART regimen, and year of ART initiation.

**Results:** Among 9,807 PWH initiating ART the cumulative incidence of achieving initial VS 6 months after ART initiation increased from 77% in 2012-2013 to 83% in 2016-2018. In multivariable analysis, factors at ART initiation significantly associated with lower rates of initial VS included age < 50 years, Black race, Northeast and South geographic region, lower CD4 count, a drug dependence/abuse diagnosis, injection drug user (IDU) transmission risk, initiating on a regimen that did not contain an integrase inhibitor (INSTI), and higher VL (Figure).

**Conclusion:** The cumulative incidence of initial VS increased over time, suggesting increased effectiveness of ART and progress towards EHE goals. Despite these gains, we identified several groups that remain less likely to achieve initial VS within 6 months. PWH of younger age, of Black race, or with a history of drug dependence/abuse or IDU transmission risk may benefit from additional HIV care and programming support to achieve VS.



**655 HIV CARE OUTCOMES AMONG AMERICAN INDIAN/ALASKA NATIVES IN THE UNITED STATES, 2018**

**Sophie Sembajwe<sup>1</sup>**, Andria Apostolou<sup>1</sup>, Jeffrey McCollum<sup>2</sup>, Azfar-E-Alam Siddiqi<sup>3</sup>, Xiaohong Hu<sup>3</sup>, Irene Hall<sup>3</sup>

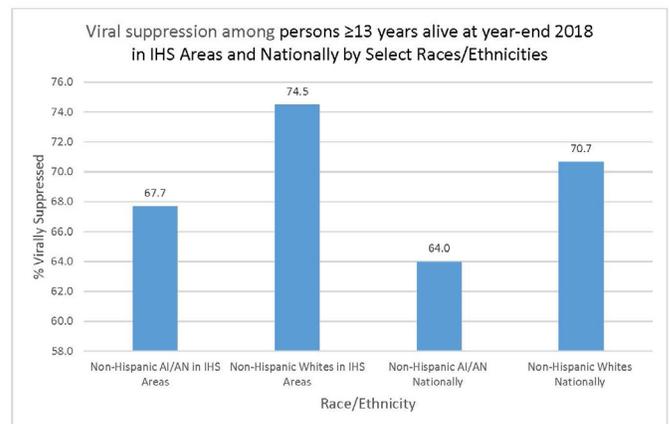
<sup>1</sup>Scimetrika, LLC; Indian Health Service, Rockville, MD, USA, <sup>2</sup>Indian Health Service, Rockville, MD, USA, <sup>3</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** In 2019, the U.S. government launched the Ending the HIV Epidemic (EHE) initiative with the aim of reducing the number of new HIV infections in the U.S. by 75%, and linking those with HIV to care and ensuring HIV viral suppression (VS) across all racial and ethnic groups to 95% by 2025. The Indian Health Service (IHS) provides federal health services to American Indian/Alaska Natives (AI/AN) who are members of the 574 federally recognized tribes consisting of 12 geographic IHS areas across the U.S. IHS is charged with fulfilling the goals of the EHE. In this analysis, we looked at differences in HIV care outcomes among non-Hispanic AI/AN compared to non-Hispanic whites based on EHE targets.

**Methods:** Using data reported to the National HIV Surveillance System (NHSS) through December 2019, we determined HIV care outcomes in 2018, for AI/AN aged ≥13 years with diagnosed HIV. Data on care outcomes were available from 41 states and the District of Columbia (DC), and analyses focused on the specific counties where IHS provides services. Linkage to HIV medical care was measured by documentation of ≥1 CD4 or viral load (VL) tests ≤1 month after HIV diagnosis in 2018. A VL test result of <200 copies/mL indicates VS. Evidence of VS among those living with diagnosed HIV was measured using the most recent VL test result in 2018.

**Results:** Among non-Hispanic AI/AN residing in IHS areas with complete laboratory data reported to NHSS in 2018, 72 (79.1%) of the 91 cases diagnosed were linked to medical care within 1 month of diagnosis. This is higher than the national percentage for non-Hispanic AI/AN (77.9%) but lower than that for non-Hispanic whites (84.4%) in IHS areas. Evidence of VS within 6 months of diagnosis was 50.5% among non-Hispanic AI/AN in IHS areas in 2018 compared to 68.4% among non-Hispanic whites. Among all 1,361 non-Hispanic AI/AN living with diagnosed HIV in IHS areas in 2018, VS was 67.7%; this is higher than national percentage for non-Hispanic AI/AN (64.0%) but lower than for non-Hispanic whites in IHS areas (74.5%).

**Conclusion:** HIV care outcomes were better among the non-Hispanic AI/AN population residing and receiving care in IHS areas compared to non-Hispanic AI/AN nationally, but fell short of percentages among non-Hispanic white residents within IHS areas. Various barriers to linkage and retention in HIV care among AI/AN need to be addressed to achieve the EHE goals of 95% linkage to care and 95% viral suppression.



**656 STRUCTURAL FACTORS ASSOCIATED WITH HIV CARE FOR BLACK PEOPLE WITH DIAGNOSED HIV, 2017**

**Joseph E. Logan<sup>1</sup>**, Nicole Crepez<sup>1</sup>, Feijun Luo<sup>1</sup>, Xueyuan Dong<sup>1</sup>, Zanetta Gant<sup>1</sup>, Allison Ertl<sup>1</sup>, Candace Girod<sup>1</sup>, Nimeshkumar Patel<sup>1</sup>, Chan Jin<sup>1</sup>, Alexandria Balaji<sup>1</sup>, Patricia Sweeney<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** Black/African American (Black) people are unequally burdened by human immunodeficiency virus (HIV) in the United States. Identifying structural social determinants of health (SDH) associated with HIV care outcomes for Black people with HIV (PWH) is critical to prevention efforts.

**Methods:** We used the World Health Organization's SDH framework and data from the National HIV Surveillance System, the U.S. Census Bureau, and the Home Mortgage Disclosure Act to examine HIV care outcomes in relation to structural SDH factors among Black PWH (n=8,520) in 42 U.S. states with complete data and laboratory reporting, aged ≥18 years, with HIV diagnosed in 2017, and alive at year-end 2018. Structural SDH factors included: exposure to racial mortgage redlining; residing in states with Medicaid expansion; and residing in states with >50% of PWH receiving Ryan White services. Outcomes included: linkage to HIV care within one month after diagnosis; and having viral suppression (<200 copies on most recent test) in 2018. Adjusted prevalence ratios (aPR) with 99% confidence intervals (99%CI) accounting for socioeconomic factors are provided.

**Results:** Just over half (50.8%) of Black people with HIV diagnosed in 2017 resided in areas with high poverty levels. The mean racial mortgage redlining index across census tracts was 2.0, indicating that Black versus White mortgage applicants were twice as likely to be rejected for mortgage loans (adjusting for loan amount, income, and gender). However, among this sample, there was no difference in the prevalence of either outcome between those residing (versus those not residing) in areas with racial mortgage redlining. For those residing (versus those not residing) in states with Medicaid expansion, linkage to HIV care within one month after diagnosis was more prevalent (aPR:1.06; 99%CI:1.02-1.10). For those residing (versus those not residing) in states with >50% of PWH receiving Ryan White services, having viral suppression in 2018 was more prevalent (aPR:1.06; 99%CI:1.02-1.11).

**Conclusion:** HIV care outcomes among Black people with HIV diagnosed in 2017 did not differ across areas with various levels of racial mortgage redlining; but, work is needed to see if redlining is concentrating Black people into low income areas thereby over-exposing them to other factors related to poor HIV care outcomes. Medicaid expansion might help PWH initiate care after diagnosis; but, ongoing services like those in the Ryan White program might be needed to achieve viral suppression.

## 657 HOUSING AND HIV OUTCOMES AMONG TRANSGENDER WOMEN IN SOUTH AFRICA

Tonia Poteat<sup>1</sup>, L Leigh Ann Van der Merwe<sup>2</sup>, Allanise Cloete<sup>3</sup>, Dee Adams<sup>4</sup>, Mannat Malik<sup>5</sup>, Andrea Wirtz<sup>6</sup>

<sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>Social Health Empowerment Feminist Collective of Transgender Women of Africa, East London, South Africa, <sup>3</sup>Human Sciences Research Council, Pretoria, South Africa, <sup>4</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>5</sup>Galgo Med, Inc, Barcelona, Spain

**Background:** Laboratory-confirmed HIV prevalence estimates among transgender women (TW) in South Africa range from 45-63% versus 20% for the general population. This analysis sought to identify intervenable factors associated with self-reported HIV infection and treatment interruptions among TW.

**Methods:** From May to September 2018, we recruited 214 TW in Cape Town, East London, and Johannesburg through community outreach. Each TW completed an interviewer-administered survey. We collected data on structural and psychosocial factors; HIV risk behaviors; self-reported HIV status; and HIV treatment. Bivariate and multivariable logistic regression models tested associations between structural (homelessness, income, hunger, sex work), interpersonal (social support, physical and sexual violence), and individual (alcohol use, medical distrust) factors and 2 outcomes: HIV status among the entire sample and inability to access antiretroviral therapy (ART) at some point in the prior 12 months among the TW living with HIV (TWLHIV).

**Results:** 31% (67/214) of TW reported being HIV+, and 31% (20/64) of TWLHIV reported inability to access ART at some point in the prior 12 months. We found significant bivariate associations between HIV status and violence, sex work, alcohol use, and homelessness. Sex work was also significantly associated with history of violence. In multivariable models, a history of homelessness [aOR 7.7; 95%CI: 3.1, 19.2] and sex work [aOR 5.7; 95%CI: 2.5, 13.2] were most strongly associated with HIV+ status. Among TWLHIV, violence, homelessness, and medical distrust were positively associated with inability to access ART, while social support was negatively associated with inability to access ART. Homelessness was the only factor that remained significant in the multivariable model, and increased odds of inability to access ART by 6-fold [aOR 6.0; 95%CI: 1.6, 22.2].

**Conclusion:** Homelessness was strongly associated with reporting HIV infection and treatment interruptions, eclipsing individual and interpersonal factors. Ensuring access to stable housing for TW is an important structural intervention that may reduce HIV risk and improve outcomes among TWLHIV. Conversely, housing discrimination may lead to homelessness among TWLHIV. Additionally, associations between sex work, violence, and HIV highlight the need for safer working conditions, including violence prevention and access to high impact HIV prevention, for TW engaged in sex work.

## 658 FOOD INSECURITY AND LOWER VIRAL SUPPRESSION IN BURMESE MIGRANTS LIVING WITH HIV

Carl Fredrik Sjöland<sup>1</sup>, Patou Musumari Masika<sup>2</sup>, Arunrat Tangmunkongvorakul<sup>3</sup>, Linda Aurbibul<sup>3</sup>, Kriengkrai Srithanaviboonchai<sup>3</sup>, Masahiro Kihara<sup>2</sup>, Susanne Rautiainen<sup>1</sup>

<sup>1</sup>Karolinska Institute, Stockholm, Sweden, <sup>2</sup>Kyoto University, Kyoto, Japan, <sup>3</sup>Chiang Mai University, Chiang Mai, Thailand

**Background:** With Thailand regarded as food secure for nearly a decade, at-risk groups including migrant workers still face food insecurity and have higher risk of acquiring HIV infection. People living with HIV and facing food insecurity have been documented to have higher risk of poor health and HIV treatment outcomes, notably altered risk behaviours and decreased adherence to antiretroviral therapy (ART). However, research on direct links between food insecurity and treatment outcomes such as viral suppression is scarce. The aim of this study was to investigate how food insecurity are associated with income, viral suppression, ART treatment and ART adherence in Burmese migrant workers living with HIV in Chiang Mai province of northern Thailand.

**Methods:** Data collected through face-to-face survey was combined with routine laboratory tests in a cohort of 316 migrants (113/203 M/F) living with HIV. 11 treatment centers for HIV in rural and urban Chiang Mai gathered data on ART use and adherence, physical and mental health, sexual behaviour, socio-demographics and food security (Household Food Insecurity Access Scale (HFAS-II)). Using a step-down multivariate logistic regression, we calculated odds ratios (OR) and 95% confidence intervals (CI), adjusting for confounders, including ART regimen.

**Results:** In this cross-sectional study, 48.7% (n=162) of migrant workers living with HIV reported food insecurity, and 14.2% (n=45) fulfilled criteria for severe food insecurity. Most respondents were ART-adherent 96.8% (n=305), and virally suppressed 93.5% (n=290), with 4.1% (n=13) expressing symptoms of clinical depression. In adjusted analysis, food insecurity was associated with lack of viral suppression [OR=4.13, CI=1.22-14.00] and perceived poverty/lack of income [OR=5.96, CI=2.58-13.76].

**Conclusion:** Burmese migrant workers living with HIV in Chiang Mai report high adherence to ART and are mostly virally suppressed. Food insecurity is here linked to viremia and poverty or lack of income, suggesting that a subset of migrants face multiple burdens that increase their likelihood of becoming viremic. With food insecurity and poverty rising as a result of the COVID-19 pandemic this may end up negatively impacting HIV treatment outcomes.

| Logistic regression<br>Food Security or insecure<br>Ref: Secure | Odds<br>ratio | 95% confidence interval | p-value |
|---|---------------|-------------------------|---------|
| Age   | 1.53          | 0.99-1.05               | 0.13    |
| Savings<br>Ref: Sufficient w/ savings                           | 2.50          | 1.14-5.46               | 0.02    |
| Sufficient, no savings  | 5.96          | 2.58-13.76              | > 0.01  |
| Insufficient  |               |                         |         |
| Sex<br>Ref: Male  | 1.33          | 0.80-2.20               | 0.27    |
| PHQ-9<br>Ref: No depressive<br>symptoms                         | 3.48          | 0.80-15.20              | 0.10    |
| Adherence<br>Ref: >95%  | 3.04          | 0.64-14.50              | 0.16    |
| Viral load<br>Ref: Suppressed                                   | 4.13          | 1.22-14.00              | 0.02    |

**659 DISTANCE TO HIV TREATMENT CENTER AND ASSOCIATION WITH ART USE AMONG MEN IN UGANDA**

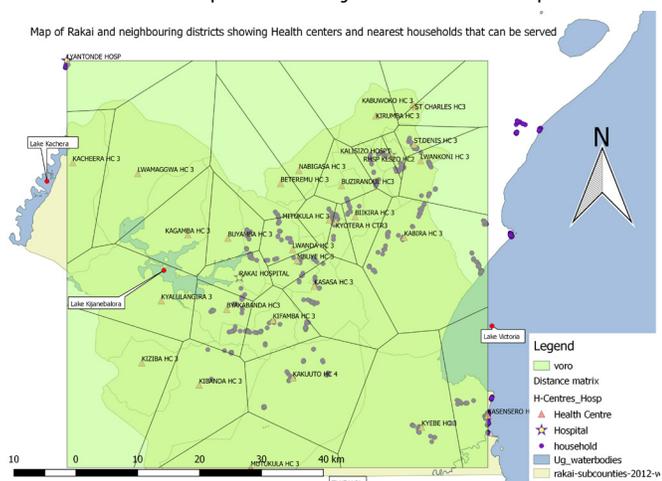
**Darix S. Kigozi<sup>1</sup>**, Fred Nalugoda<sup>1</sup>, Godfrey Kigozi<sup>1</sup>, Victor Ssempijja<sup>1</sup>, Hadijja Nakawooya<sup>1</sup>, Joseph Kagaayi<sup>1</sup>, Anthony Ndyanabo<sup>1</sup>, Tom Lutalo<sup>1</sup>, David Sserwadda<sup>2</sup>, Steven Reynolds<sup>3</sup>, Lisa Mills<sup>4</sup>, Michelle Adler<sup>4</sup>, Ronald Gray<sup>5</sup>  
<sup>1</sup>Rakai Health Sciences Program, Kalisizo, Uganda, <sup>2</sup>Makerere University College of Health Sciences, Kampala, Uganda, <sup>3</sup>National Institute of Allergy and Infectious Diseases, Baltimore, MD, USA, <sup>4</sup>Centers for Disease Control and Prevention, Kampala, Uganda, <sup>5</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Background: There is underutilization of antiretroviral therapy (ART) among HIV positive men but more pronounced among adolescent and young adults (AYA) aged 15–24 years, compared to adult men (25–49 years). We used Geo Spatial data to determine the distance to the nearest treatment center from each home of an HIV-positive male respondent. We examined the association of distance to ART initiation in a community-based cohort in south central Uganda.

**Methods:** Method: We analyzed data from the Rakai Community Cohort Study (RCCS) for HIV-positive men between 2016 and 2018. We used GPS data and QGIS software to estimate the distance in Coordinate Reference System (CRS) units between each place of residence and the nearest treatment center offering ART services. Ever initiated on ART was the outcome variable and distance the major predictor variable. Other covariates included: community type (fishing, trading or agrarian), marital status, religion, occupation, alcohol consumption, education, mobility and number of sexual partners. We used a Poisson GLM to establish the relative risk associated with ART initiation. ART for key populations in fishing communities was initiated using test and treat, whereas other communities initiated ART based on CD4 levels.

**Results:** Results: The analysis included HIV positive men (N=1,289), ever initiated on ART (n=971), never on ART (n=318). From the spatial pattern, the mean distance to health centers is 0.05 in CRS units. Distance to health centers was not statistically associated with ART initiation. The relative risk of not being on ART was increased among the youth (15-24 years) compared to older men (RR: 1.68; CI 1.06, 2.67). There was an increased risk of non-ART use among men who were either divorced or never married compared to those currently married (RR: 1.60; CI 1.00, 2.54) and (1.55; CI 1.19, 2.01), respectively. There was increased risk among residents from non-fishing communities compared to the fishing communities and the immigrants compared to the more permanent (RR: 1.69; CI 1.21- 2.38); (RR: 1.64; CI 1.29- 2.09) resp.

**Conclusion:** Conclusion: There is no evidence that distance to treatment facilities affects ART initiation among men. However, ART use among young unmarried men, immigrants and those residing outside fishing communities is low. Test and treat provided in fishing communities increased uptake of ART.



**660 REASONS FOR NONDISCLOSURE OF HIV-POSITIVE STATUS TO HEALTH CARE PROVIDERS, MOZAMBIQUE**

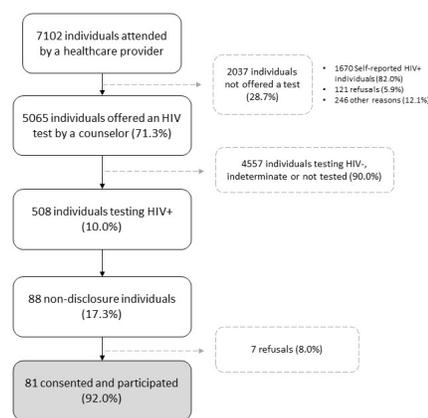
**Laura Fuente-Soro<sup>1</sup>**, Antía Figueroa-Romero<sup>1</sup>, Sheila Fernández-Luis<sup>1</sup>, Orvalho Augusto<sup>2</sup>, Elisa Lopez-Varela<sup>1</sup>, Edson Bernardo<sup>2</sup>, Paula Paz<sup>3</sup>, Stanley C. Wei<sup>4</sup>, Peter Kerndt<sup>4</sup>, Tacita Nhampossa<sup>2</sup>, Denise Naniche<sup>1</sup>  
<sup>1</sup>Barcelona Institute for Global Health, Barcelona, Spain, <sup>2</sup>Manhiça Health Research Centre, Manhiça, Mozambique, <sup>3</sup>Fundação Ariel Glaser Contra o SIDA Pediátrica, Maputo, Mozambique, <sup>4</sup>Centers for Disease Control and Prevention, Maputo, Mozambique

**Background:** In settings where provider-initiated HIV counseling and testing (PICT) is the main approach to identify new HIV cases, nondisclosure of HIV-positive status or prior testing to clinicians may lead to re-testing and, consequently, waste of scarce resources and distorted estimates of persons who know their HIV-positive status. In 2015 in Mozambique, an estimated one-third of people tested HIV positive but already knew their status. To our knowledge, our study is the first to assess the barriers that prevent people living with HIV (PLHIV) from disclosing their HIV-positive status to healthcare providers during a PICT testing campaign.

**Methods:** This analysis was nested in a larger PICT cross-sectional study performed in the Manhiça District, southern Mozambique in 2019, in which healthcare providers actively asked patients about their HIV status. The identity of patients who tested positive was crosschecked with the hospital database to detect current or previous enrolment in care. PLHIV who did not disclose their HIV-positive status were invited to participate and responded to a questionnaire designed to explore barriers, patterns of community/family disclosure, and stigma and discrimination

**Results:** Our results showed that 17.3% of participants who tested positive during a PICT campaign already knew their HIV status and had enrolled in care but did not disclose it to the PICT campaign healthcare provider. Of participants, 92% reported previous mistreatment by general healthcare providers as a reason for nondisclosure during PICT (Figure). Other reasons included the desire to confirm if they were cured (33.3%) or to re-engage in care (23.5%). Among respondents, 83.9% reported having disclosed their HIV status within their close community, 27.2% reported being victims of verbal or physical discrimination, and 46.7% reported that their HIV status affected their daily activities

**Conclusion:** Previous mistreatment by healthcare workers was the main barrier to disclosing HIV status. The high proportion of those disclosing their HIV status to their community but not to healthcare providers suggests that challenges with patient-provider relationships affect this care behavior rather than general stigma and discrimination. Improving patient-provider relationships could increase trust in healthcare providers, reduce nondisclosures, and help optimize resources and accurate estimates of PLHIV aware of their HIV-positive status



**661 DEPRESSION AND HIGHER EDUCATION ARE DRIVERS OF HIV STIGMA IN A SOUTH AFRICAN TOWNSHIP**

**Megan F. Meyer<sup>1</sup>**, Paul K. Drain<sup>1</sup>, Sean Galagan<sup>1</sup>, Sabina Govere<sup>2</sup>, Bernadette Gosnell<sup>3</sup>, Mahomed-Yunus Moosa<sup>3</sup>  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>AIDS Healthcare Foundation, Durban, South Africa, <sup>3</sup>University of KwaZulu-Natal, Durban, South Africa

**Background:** HIV stigma remains a significant barrier to HIV testing and engagement in care. Despite expanded access to HIV treatment, HIV-related

stigma has not declined in LMICs. We measured the prevalence of HIV-related stigma, and identified sociodemographic and clinical factors associated with stigmatizing attitudes (negative attitudes towards individuals who may be HIV positive) and anticipated stigma (the expectation of experiencing prejudice and stigmatizing behaviors if the respondent became HIV positive).

**Methods:** We conducted a cohort study of adults seeking HIV testing between 2013 and 2018 in Umlazi township, South Africa. We used a validated HIV stigma scale consisting of seven questions about stigmatizing attitudes and five questions about anticipated stigma and obtained survey responses prior to HIV testing. We coded responses to each question 0–2 (0=no stigma, 1=mild stigma, 2=high stigma) to calculate an overall stigma score and categorized participants as either having "no stigma" or "mild or high stigma". We used multivariate logistic regression to identify statistically significant sociodemographic and clinical correlates of holding stigmatizing attitudes or having anticipated stigma.

**Results:** 7,724 (98.0%) of 7,877 participants enrolled completed the 12-question stigma scale. 1,318 (16.9%) reported at least one stigmatizing attitude and 2,396 (30.8%) reported at least one anticipation of stigma. In separate adjusted multivariate models, the strongest predictors of having both stigmatizing attitudes and anticipated stigma were having depressive symptoms ("stigmatizing attitudes" adjusted odds ratio (aOR)= 19.49 and "anticipated stigma" aOR= 9.34) and having attended University ("stigmatizing attitudes" aOR= 6.89 and "anticipated stigma" aOR= 7.00) (Table). Additional significant predictors of HIV-stigma included employment, female sex, younger age, single status, not attending church, and having a partner that had not tested for HIV or had tested negative for HIV.

**Conclusion:** In an urban township of South Africa, both stigmatizing attitudes and perceived stigma continue to be common. Having attended university and having depressive symptoms appear to be important risk factors for holding stigmatizing attitudes and for anticipating HIV stigma against oneself. Addressing HIV-stigma among those who may need greater support following a diagnosis of HIV may be important for improving HIV treatment outcomes.

Table. Adjusted odds ratios of reported stigmatizing attitudes and anticipated stigma by sociodemographic characteristics

| Sociodemographic Characteristics | Stigmatizing Attitudes (N=7,736) |         | Anticipated stigma (N=7,284) |         |
|----------------------------------|----------------------------------|---------|------------------------------|---------|
|                                  | aOR (CI)                         | P-value | aOR (CI)                     | P-value |
| <b>Sex</b>                       |                                  |         |                              |         |
| Female                           | 1.09 (0.94 – 1.26)               | 0.278   | 1.23 (1.09 – 1.39)           | <0.001  |
| Male                             | 1.0                              | --      | 1.0                          | --      |
| <b>Age</b>                       |                                  |         |                              |         |
| 18-25                            | 1.13 (0.84 – 1.50)               | 0.421   | 1.52 (1.18 – 1.95)           | <0.001  |
| >45                              | 1.0                              | --      | 1.0                          | --      |
| <b>Marital Status</b>            |                                  |         |                              |         |
| Single                           | ..a                              | --      | 1.84 (1.38 – 2.46)           | <0.001  |
| Married                          | 1.0                              | --      | 1.0                          | --      |
| <b>Church Attendance</b>         |                                  |         |                              |         |
| No                               | ..a                              | --      | 1.41 (1.23 – 1.62)           | <0.001  |
| Yes                              | 1.0                              | --      | 1.0                          | --      |
| <b>Education</b>                 |                                  |         |                              |         |
| University                       | 6.89 (4.79 – 9.90)               | <0.001  | 7.00 (5.04 – 9.73)           | <0.001  |
| None                             | 1.0                              | --      | 1.0                          | --      |
| <b>Depressive symptoms</b>       |                                  |         |                              |         |
| Yes                              | 19.49 (16.61 – 22.88)            | <0.001  | 9.34 (7.89 – 11.05)          | <0.001  |
| No                               | 1.0                              | --      | 1.0                          | --      |
| <b>Employment</b>                |                                  |         |                              |         |
| Yes                              | 1.52 (1.26 – 1.84)               | <0.001  | 1.24 (1.10 – 1.40)           | <0.001  |
| No                               | 1.0                              | --      | 1.0                          | --      |
| <b>Partner Tested for HIV</b>    |                                  |         |                              |         |
| No                               | 1.10 (0.90 – 1.35)               | 0.327   | 1.79 (1.50 – 2.13)           | <0.001  |
| Yes, HIV (-)                     | 0.89 (0.71 – 1.12)               | 0.307   | 1.67 (1.38 – 2.02)           | <0.001  |
| Yes, HIV (+)                     | 1.0                              | --      | 1.0                          | --      |

Note. aOR=adjusted odds ratio; CI=95% confidence intervals. The adjusted model for stigmatizing attitudes also included income, HIV status, and visit to a traditional healer within the last six months. The adjusted model for anticipated stigma also included HIV status and children.

<sup>a</sup> Marital status and attendance to church were not significant in the unadjusted model and were not included in the adjusted model.

**662 THE TREATMENT GAP FOR MENTAL DISORDERS IN PEOPLE LIVING WITH HIV IN SOUTH AFRICA**

**Yann Ruffieux<sup>1</sup>, Orestis Efthimiou<sup>1</sup>, Leigh Van den Heuvel<sup>2</sup>, John Joska<sup>3</sup>, Morna Cornell<sup>3</sup>, Soraya Seedat<sup>2</sup>, Hannes Mouton<sup>3</sup>, Hans Prozesky<sup>2</sup>, Crick Lund<sup>3</sup>, Nicky Maxwell<sup>3</sup>, Mpho Tlali<sup>3</sup>, Catherine Orrell<sup>3</sup>, Mary-Ann Davies<sup>3</sup>, Gary Maartens<sup>3</sup>, Andreas D. Haas<sup>1</sup>**

<sup>1</sup>Institute of Social and Preventive Medicine, Bern, Switzerland, <sup>2</sup>Stellenbosch University, Cape Town, South Africa, <sup>3</sup>University of Cape Town, Cape Town, South Africa

**Background:** Mental disorders are common in people living with HIV (PLWH) but often remain untreated. This study aimed to explore the gap in access to treatment ("treatment gap") for mental disorders in adults followed-up in antiretroviral therapy (ART) programs in South Africa and to identify disparities between these programs in terms of access to mental health services.

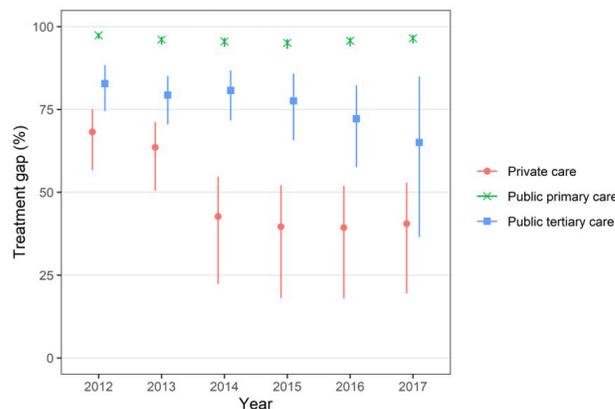
**Methods:** We conducted a cohort study using linked pharmacy and hospitalization data from one private care, two public primary care, and one

public tertiary care ART programs in South Africa. We restricted our study to adults aged 15–49 years. Patients were followed-up from January 1, 2012 to December 31, 2017. We estimated the proportion of patients treated for a mental disorder (pharmacological or inpatient) in the ART programs in each calendar year, and examined factors associated with the rate of treatment for mental disorders in those programs. We calculated the treatment gap for mental disorders as the discrepancy between the 12-month prevalence of mental disorders in PLWH in South Africa (based on data from the Global Burden of Disease study) and the proportion of patients treated for a mental disorder in the ART programs in each calendar year. We calculated adjusted rate ratios (aRR) for factors associated with the rate of treatment of mental disorders using Poisson regression.

**Results:** 182,285 ART patients were followed-up over 405,153 person-years. In 2017, the estimated treatment gap for mental disorders was 40.5% (95% CI 19.5%–52.9%) for patients followed-up in private care, 96.5% (95% CI 95.0%–97.5%) for patients followed-up in public primary care, and 65.0% (95% CI 36.5%–85.1%) for patients followed-up in public tertiary care ART programs (Figure). Rates of treatment with antidepressants, anxiolytics and antipsychotics were 17 (aRR 0.06, 95% CI 0.06–0.07), 50 (aRR 0.02 95% CI 0.01–0.03), and 2.6 (aRR 0.39, 95% CI 0.35–0.43) times lower in public primary care programs than in the private sector ART program.

**Conclusion:** There is a large treatment gap for mental disorders in PLWH in South Africa. We found substantial disparities in access to mental health service between patients receiving ART in the public vs. the private sector. In the public sector and especially in public primary care, common mental disorders remain largely untreated in PLWH.

The treatment gap for mental disorders in private care, public primary care and public tertiary care HIV programs in South Africa, 2012–2017.



**663 HEALTH DISPARITIES DUE TO NONADHERENCE TO ANTIPSYCHOTICS IN PLWH WITH SCHIZOPHRENIA**

**Sony Subedi<sup>1</sup>, Ni Gusti Ayu Nanditha<sup>1</sup>, Hiwot Tafessu<sup>1</sup>, Martin St-Jean<sup>1</sup>, Julius Elefante<sup>2</sup>, Thomas L. Patterson<sup>3</sup>, William G. Honer<sup>4</sup>, Julio S. Montaner<sup>1</sup>, Viviane D. Lima<sup>1</sup>**

<sup>1</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, <sup>2</sup>St Paul's Hospital, Vancouver, Canada, <sup>3</sup>University of California San Diego, San Diego, CA, USA, <sup>4</sup>University of British Columbia, Vancouver, Canada

**Background:**

Non-adherence to antipsychotics is the greatest obstacle to treating schizophrenia, and it is likely to exacerbate the clinical implications of HIV and its treatment. We assessed the economic and clinical impact of non-adherence to antipsychotics among people living with HIV/AIDS (PLWH) and schizophrenia in British Columbia, Canada.

**Methods:**

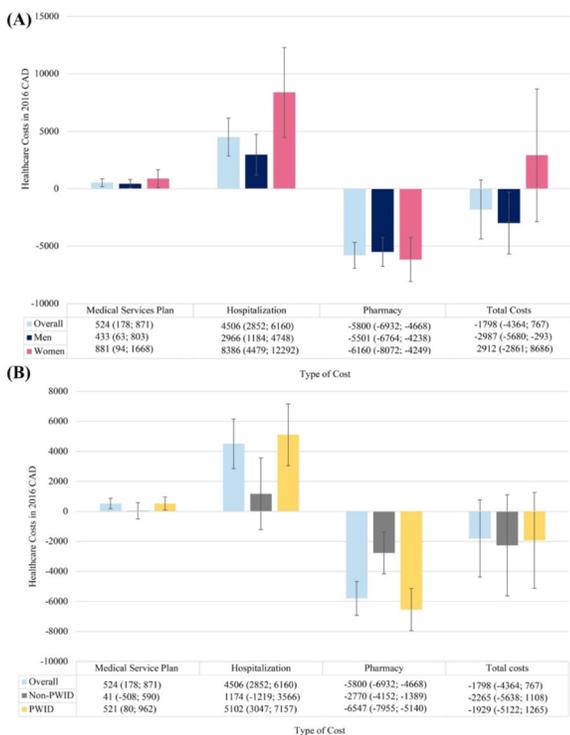
Eligible individuals were in the STOP HIV/AIDS cohort during 2001–2016, diagnosed with schizophrenia, on antipsychotics for ≥1 day, and followed for ≥1 year from schizophrenia diagnosis date or January 1, 2001, whichever occurred last. Adherence to antipsychotics was measured using the proportion of days covered methodology. A Two-Part model assessed the marginal effect of adherence on healthcare costs (in 2016 CAD), including hospitalizations, physician visits and medication dispensations. Logistic regression or generalized linear mixed models examined the effect on virologic failure (viral load >200

copies/mL), hospital readmissions within 30 days, and length of hospital stay. Models were adjusted for several confounders.

**Results:** Among 726 PLWH with schizophrenia, ≥80% adherence to antipsychotics increased from 34% in 2001 to 55% in 2016. We observed no difference in adherence to antipsychotics among those who used only injectable form, only non-injectable form, and a combination of both. Similarly, no difference in adherence was observed among individuals who have ever consumed typical/first-generation antipsychotics and those who consumed only atypical/second-generation antipsychotics. We observed that individuals with poor adherence to antipsychotics were also poorly adhered to antiretrovirals, especially in the earlier study years. Compared to adherent individuals, annual hospitalization and physician visit costs were higher among non-adherent individuals (\$5030), particularly among women (\$8386) and people who ever injected drugs (\$5102) (Figure 1). Non-adherent individuals also experienced higher virologic failure (adjusted Odds Ratio [aOR]=1.65, 95% 95%CI: 1.06-2.56), more hospital readmissions (aOR=1.52, 95%CI: 1.29-1.79), and longer hospital stays (adjusted Mean Ratio=1.51, 95%CI: 1.39-1.64).

**Conclusion:** Our results showed that implementing strategies and interventions to increase antipsychotic adherence, focusing on women and people who have ever injected drugs, will be critical in addressing this public health challenge.

**Figure 1.** Marginal effect on annual healthcare costs among non-adherent PLWH with schizophrenia compared to their adherent counterparts in our study population, overall and stratified by (A) Gender and (B) People who have ever injected drugs (PWID) status (adjusted to 2016 CAD).



**664 OPIOID USE DISORDER, AGONIST THERAPY, AND MORTALITY AMONG PEOPLE LIVING WITH HIV**

**Nalin Dhillon<sup>1</sup>, Audrey G. Tung<sup>1</sup>, Jason Trigg<sup>1</sup>, Martin St-Jean<sup>1</sup>, Viviane D. Lima<sup>1</sup>, Ni Gusti Ayu Nanditha<sup>1</sup>, Julio S. Montaner<sup>1</sup>, Rolando Barrios<sup>1</sup>, Kate Laird<sup>1</sup>, Monica Ye<sup>1</sup>, Cole Stanley<sup>1</sup>, Taylor McLinden<sup>1</sup>, Kate Salters<sup>1</sup>**

<sup>1</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada

**Background:** British Columbia's (BC's) overdose crisis has had devastating impacts on the general population, but little is known on how it has affected People living with HIV (PLWH). We therefore characterized the annual crude mortality rates for overdose-related deaths, and examined potential risk and protective factors for overdose-related mortality in our population.

**Methods:** Using the BC STOP HIV/AIDS database, we examined overdose-related deaths among PLWH in BC, Canada who were followed for >6 months

between April 1, 2009-March 31, 2017 in BC, Canada. Overdose-related deaths were ascertained using ICD-10 codes in the Vital Statistics registry. Confounder-adjusted logistic regression models examined whether opioid use disorder (OUD) diagnoses (defined as an ever-recorded OAT dispensation, ever ≥ 3 physician claims, or 1 hospital admission) and opioid agonist therapy (OAT) prescriptions were associated with overdose-related mortality.

**Results:** Of 9594 PLWH in BC during the study period, 166 (18%) died of overdose-related causes. The crude period mortality rate was 2.89 deaths per 1,000 person-years (PY), with women experiencing 1.81 times higher rates of overdose-related mortality. Annual mortality rates began increasing in 2012/13 to a high of 5.1 deaths per 1,000 PY in 2016/17. Of those who died from overdose, 75% met the prescription criteria for OAT, while 51% did not receive an OAT prescription. Women were significantly more likely to be prescribed neuropathic pain relievers (NPRs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and sedatives. After adjustment for health authority, gender, HCV co-infection status, diagnosis of a mental health illness, date of most recent OAT prescription, and age at death, people who were diagnosed with OUD has 3.48x the odds of dying of overdose compared to all causes of death, while the absence of OAT was non-significantly associated with risk of overdose deaths (AOR: 1.09, 95% CI: 0.70-1.7).

**Conclusion:** Overdose-related mortality among PLWH, which has been increasing amid the opioid crisis, is significantly correlated to chronic prescription trends and OUD, and non-significantly associated with the absence of OAT. Further research into these factors, particularly as mediated by OAT, may shed light on vulnerabilities related to prescription practices, drug interactions with OAT medications, and missed opportunities for OAT.

**665 SEXUAL HEALTH SERVICES FOR PEOPLE WHO ENGAGE IN EXCHANGE SEX: NEEDS AND OPPORTUNITIES**

**Medhavi Bole<sup>1</sup>, Christine Khosropour<sup>1</sup>, Matthew R. Golden<sup>1</sup>, Sara Glick<sup>1</sup>, Lindley Barbee<sup>1</sup>, Shireesha Dhanireddy<sup>1</sup>, Julia C. Dombrowski<sup>1</sup>**

<sup>1</sup>University of Washington, Seattle, WA, USA

**Background:** People who exchange sex (PWES) for money or drugs are at increased risk of HIV and other sexually transmitted infections (STIs) and may need tailored prevention and care services. Our objective was to characterize patients in the Public Health - Seattle & King County (PHSKC) - Sexual Health Clinic who reported engaging in exchange sex and identify opportunities for improved service.

**Methods:** We conducted a cross-sectional analysis of patient encounters for new problem visits October 2010 - March 2020 with a completed computer assisted self-interview including sex assigned at birth, gender identity, and receipt of money or drugs for sex, ever or in the past year. Visits were the unit of analysis. We analyzed demographics, STI and HIV history, Hepatitis C (HCV) testing and treatment history, PrEP use, and reason for visit among encounters in which the patient reported ever exchanging sex, stratified by gender. Our analysis focused on people who reported a lifetime history of exchange sex because the characteristics of this group did not differ substantially from people who reported exchanging sex in the past year. We compared characteristics of PWES ever vs never using chi square tests.

**Results:** During the study period 30,327 unique patients attended 64,680 clinic visits. At these visits, 1,470 (2%) reported exchange sex in the past 12 months and 3,097 (5%) reported ever exchanging sex, among whom 1,943 (63%) were cis-men, 969 (31%) were cis-women, and 185 (6%) were transgender persons. Among PWES, the most common reason for coming to clinic was wanting a STI test (61%), HIV test (45%), or STI symptoms (40%). Compared to patients who never exchanged sex, PWES were more likely to report homelessness, injection drug use (IDU), STIs in the past 12 months, and a prior diagnosis of HIV or HCV (Table 1). Among PWES, homelessness was more common among cis-women (33%) compared to cis-men (21%) and transgender persons (18%), and IDU was higher among cis-men (42%), than cis-women (33%), and transgender persons (29%). More cis-men reported >5 sexual partners (53%) or an STI (51%) in the past year compared to cis-women (16% and 26%, respectively). Among PWES who did not have a prior HIV diagnosis, 17% were on PrEP (22% of cis-men, 1% of cis-women, 43% of transgender).

**Conclusion:** Many PWES in the Sexual Health Clinic had complex barriers to care including homelessness and IDU, and higher percentage of STIs, HIV, and HCV. Clinic visits are an opportunity to increase PrEP use and HCV treatment for PWES.

**Table 1:** Characteristics of patient visits attending the PHSKC Sexual Health Clinic

| Characteristic                | Total<br>n (%)<br>64,680 (100) | Never exchanged sex<br>n (%)<br>61,583 (95) | Exchange sex ever<br>n (%)<br>3,097 (5) | p-value |
|-------------------------------|--------------------------------|---|---|---------|
| Homeless, past 12 months      | 1,997 (6)                      | 1,617 (5)                                   | 380 (23)                                | <0.001  |
| IDU, past 12 months           | 3,507 (5)                      | 2,325 (4)                                   | 1,182 (38)                              | <0.001  |
| STI diagnosis, past 12 months | 16,218 (30)                    | 15,077 (29)                                 | 1,141 (43)                              | <0.001  |
| Prior HIV diagnosis           | 4,094 (6)                      | 3,655 (6)                                   | 439 (14)                                | <0.001  |
| Prior HCV diagnosis           | 1,657 (3)                      | 1,249 (2)                                   | 408 (13)                                | <0.001  |
| Received HCV Treatment*       | 516 (31)                       | 429 (34)                                    | 87 (21)                                 | <0.001  |
| Ever on PrEP                  | 9,446 (15)                     | 8,921 (14)                                  | 525 (17)                                | 0.110   |

\*Among those with prior HCV diagnosis

## 666 METHAMPHETAMINE USE AND HIV/STI RISK AMONG USERS OF SUBSTANCE USE TREATMENT PROGRAMS

Jessica Sherman<sup>1</sup>, Christina Dyar<sup>2</sup>, Ethan Morgan<sup>1</sup>

<sup>1</sup>The Ohio State University, Columbus, OH, USA, <sup>2</sup>Northwestern University, Chicago, IL, USA

**Background:** In recent years, methamphetamine use has been on the rise in the United States. At the same time, the rates of many sexually transmitted infections (STIs) have risen sharply, including gonorrhea, chlamydia, and syphilis. In this analysis, we sought to ascertain whether the risk of STIs and HIV among methamphetamine users differs on the basis of participation in substance use treatment programs.

**Methods:** Data came from the nationally representative, public dataset, the National Survey on Drug Use and Health (NSDUH), 2015–2019. Among adult participants, survey-weighted logistic regression analyses were used to assess the relationship between past year methamphetamine use and risk of HIV and STIs. Analyses were stratified by methamphetamine treatment utilization in the past year and adjusted for demographic and other risk factors.

**Results:** Among participants in the analytic sample (N = 207,913), 2,034 (1.0%) reported past year methamphetamine use, 599 (0.3%) reported receiving treatment for its use, 6,158 (3.0%) tested positive for any STI in the past year, and 419 (0.2%) for HIV ever in their lifetime. Weighted estimates produced 1.74 million methamphetamine users per year, 510,542 who sought treatment for methamphetamine use in the past year, 5.22 million with any STI in the past year, and 535,617 with HIV in their lifetime. In analyses stratified by treatment use, past year methamphetamine use was associated with increased risk of STIs among those who did not receive treatment (adjusted odds ratio [aOR] = 3.63; 95% confidence interval [CI]: 2.71, 4.85) and among those who did receive treatment (aOR = 2.20; 95% CI: 1.02, 4.72). Regarding HIV, past year methamphetamine use was associated with increased risk of infection among those not receiving treatment (aOR = 8.64; 95% CI: 4.99, 14.96) while no significant difference in risk based on methamphetamine use was observed among those who did not receive treatment in the past year.

**Conclusion:** In this analysis, we demonstrated a strong relationship between methamphetamine use and risk of HIV and STIs that differed based on receipt of treatment for methamphetamine use. Notably, the risk of STIs associated with methamphetamine use was lower among those who received treatment for methamphetamine use compared to those who did not. These findings suggested that integrated STI, HIV, and substance use treatment programs may yield substantial public health benefits.

## 667 CANNABIS USE ASSOCIATED WITH DECREASED ART ADHERENCE IN AGING PEOPLE WITH HIV

Jennifer A. Manuzak<sup>1</sup>, Janeway Granche<sup>2</sup>, Katherine Tassiopoulos<sup>2</sup>, Ronald J. Ellis<sup>3</sup>, Karl Goodkin<sup>4</sup>, Anjali Sharma<sup>5</sup>, Kristine Erlandson<sup>6</sup>, for the ACTG A5322 Study Team

<sup>1</sup>Tulane National Primate Research Center, Covington, LA, USA, <sup>2</sup>Harvard TH Chan School of Public Health, Boston, MA, USA, <sup>3</sup>University of California San Diego, La Jolla, CA, USA, <sup>4</sup>University of Nebraska Medical Center, Omaha, NE, USA, <sup>5</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>6</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA

**Background:** Cannabis is commonly used in the United States, particularly among people with HIV (PWH). Conflicting evidence exists on the impact of cannabis use on care of PWH, particularly among older adults. Here, we leveraged data collected through ACTG A5322, an observational study of PWH ≥40 years in long-term follow-up, to longitudinally characterize associations between cannabis use and antiretroviral therapy (ART) adherence.

**Methods:** A5322 participants with ≥2 substance use surveys were included. At each visit, participants were categorized as 100% ART adherent if they

indicated no missed doses of antiretroviral medication within the past 7 days, and as <100% adherent otherwise; visits during which participants were not on ART were excluded. Cannabis use was updated at each visit; participants were categorized as current cannabis users if they reported use within the past month, intermittent users if they reported use within the past year but >1 month ago, and non-users if they reported use ≥1 year ago or never. Generalized linear models using generalized estimating equations (GEE) were fit. Inverse probability weighting (IPW) was used to adjust for static and time-varying confounders and drop-out.

**Results:** A total of 963 participants contributed up to 6 years of data. At A5322 entry, 18% reported current cannabis use, 6% intermittent use, and 76% non-use; 88% reported 100% ART adherence. Mean age at entry was 51 years, 81% were male at birth, and 49% identified as White non-Hispanic, 30% as Black non-Hispanic, 18% as Hispanic and 2% another race/ethnicity. Participants who were cannabis users and reported current use were more likely to be <100% ART adherent than non-users (adjusted relative risk [aRR]=1.65, CI95=1.26, 2.16) and intermittent users (aRR=1.68, CI95=1.01, 2.81) (Table). There was no association between intermittent vs non-use and ART adherence (aRR=0.98, CI95=0.61, 1.57).

**Conclusion:** Current cannabis-using PWH had a higher risk of being <100% adherent to their ART regimen when compared to intermittent and non-users. These findings have clinical implications, as poor ART adherence is associated with less effective viral suppression, drug resistance and comorbidities. Further research is needed to elucidate the underlying biobehavioral mechanisms by which cannabis use elicits decreased ART adherence in older PWH and the downstream impacts on risk for comorbid conditions.

**Table:** Adjusted association between cannabis use and ART non-adherence

| Cannabis use group             | Unadjusted Model    |         | Weight* Adjusted Model |         |
|--------------------------------|---------------------|---------|------------------------|---------|
|                                | Risk Ratio (95% CI) | P-value | Risk Ratio (95% CI)    | P-value |
| Current user (vs non-user)     | 1.85 [1.49, 2.31]   | <.01    | 1.65 [1.26, 2.16]      | <.01    |
| Current user (vs intermittent) | 1.43 [0.97, 2.11]   | 0.07    | 1.68 [1.01, 2.81]      | 0.05    |
| Intermittent (vs non-user)     | 1.30 [0.88, 1.91]   | 0.19    | 0.98 [0.61, 1.57]      | 0.94    |

\*Stabilized inverse probability weights adjusting for drop-out, static covariates (sex, race/ethnicity, education level, smoking status, years on ART), and time-varying covariates (alcohol use, non-cannabis substance use, physical activity level).

## 668 A WEB TOOL TO PROJECT LOCAL IMPACT OF INTERVENTIONS TO END HIV EPIDEMICS IN THE US

Anthony T. Fojo<sup>1</sup>, Melissa Schnure<sup>2</sup>, Parastu Kasaie<sup>2</sup>, David Dowdy<sup>2</sup>, Maunank Shah<sup>1</sup>

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

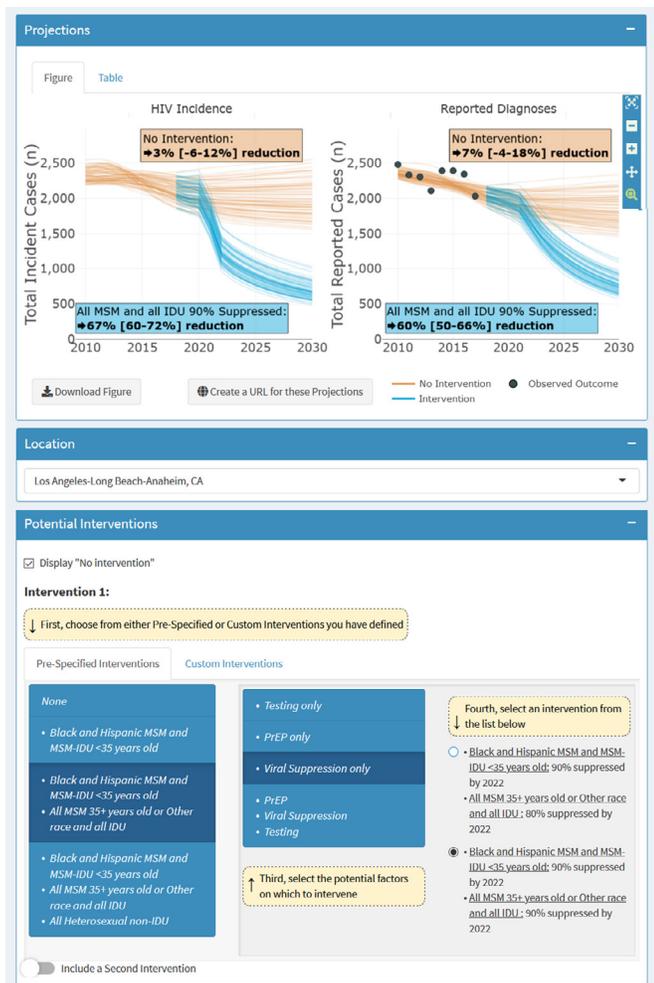
**Background:** The Ending the HIV Epidemic (EHE) Initiative aims to reduce HIV incidence by 90% by 2030 through a combination of rapidly diagnosing new HIV infections, preventing infection in susceptible populations through interventions such as pre-exposure prophylaxis (PrEP), and treating people with HIV (PWH) to achieve viral suppression. HIV epidemics are localized in nature, and the levels of testing, PrEP, and viral suppression needed to achieve EHE goals in specific locations are unclear. A user-friendly, location-specific tool to address this question could aid HIV decision-makers in choosing pathways to reach EHE goals.

**Methods:** The Johns Hopkins Epidemiological and Economic Model (JHEEM) is a dynamic, compartmental model representing the HIV epidemic, calibrated to 32 Metropolitan Statistical Areas (MSAs) which encompass the 48 high-burden counties plus Washington DC identified by the EHE plan. The model makes projections of incidence, prevalence, reported diagnoses, and mortality for interventions that combine three parameters: (1) the frequency of HIV testing, (2) the proportion of at-risk individuals who are enrolled in PrEP program, and (3) the proportion of PWH who are virally suppressed. These interventions can be targeted to demographic strata of age (13–24, 25–34, 35–44, 45–54, and ≥55 years old), race (Black, Hispanic, Other), sex (male, female), and HIV acquisition risk factor (men who have sex with men, injection drug users, heterosexuals). The interactive web tool allows users to visualize model projections for potential interventions in any of the 32 MSAs. Additionally, users can design custom interventions combining different levels of HIV testing, PrEP, and viral suppression, and run simulations to evaluate these interventions in real time.

**Results:** The web tool is publicly available at [www.jheem.org](http://www.jheem.org), with data visualizations as shown in the Figure. In order to achieve the EHE goal of reducing incidence by 90% over a decade, most MSAs are projected to require

interventions that target multiple demographic strata and combine yearly HIV testing, PrEP uptake of 25-50% in at-risk individuals, and viral suppression of 80-90% across key populations.

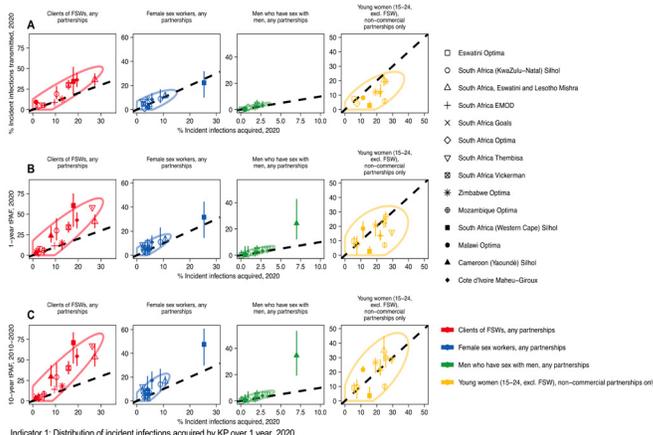
**Conclusion:** The EHE goal of 90% reduction in HIV incidence is achievable, but will require substantial improvements in HIV testing, PrEP, and viral suppression among PWH. Our publicly available web tool allows health officials to project which interventions are most likely to achieve EHE goals in their local environment.



**Results:** Estimates of the 10-year tPAF (Fig.C) were consistently greater than the 1-year tPAF (Fig.B), which was greater than the % HIV infections transmitted in 1 year for each KP (Fig.A), reflecting increasing numbers of secondary transmissions captured by each indicator. For FSW, their clients and MSM, the acquisition indicator was consistently lower than the three transmission indicators. Whereas for young women, the acquisition indicator tended to be larger, suggesting that they acquire more infections than they transmit. Agreement on the greatest KP contributor across all indicators was rare (3 models), even for indicators related to % incident infections acquired/transmitted (4 models), but more common for the 1-year/10-year tPAFs (13 models).

**Conclusion:** Using one indicator is insufficient to fully characterize the contribution of KP resulting from HIV prevention/treatment gaps in the settings explored. Distributions of HIV acquisition and longer-term tPAF appear to most appropriately reflect the relative contribution of different KP across diverse African HIV epidemics.

Figure: Correlation plots for the fraction of HIV infections acquired by each KP in 2020 and A) fraction of HIV infections transmitted by each KP in 2020 B) 1-year tPAF 2020 C) 10-year tPAF 2010-2020, from models of HIV transmission in Africa. Dotted black line represent equivalence of indicators, while circles indicate the 95% confidence interval.



Indicator 1: Distribution of incident infections acquired by KP over 1 year, 2020  
 Indicator 2: Distribution of incident infections transmitted by KP over 1 year, 2020  
 Indicator 3: tPAF over 1 year, 2020 (proportion of infections prevented over 1 year if no transmission occurs from KP to any of their partners in partnerships indicated)  
 Indicator 4: tPAF over 10 years, 2010-2020 (proportion of infections prevented over 10 years if no transmission occurs from KP to any of their partners in partnerships indicated)

**669 MODEL-BASED COMPARISON OF THE CONTRIBUTION OF KEY POPULATIONS TO HIV EPIDEMICS**

Ross D. Booton<sup>1</sup>, Kate M. Mitchell<sup>2</sup>, James Stannah<sup>3</sup>, Romain Silhol<sup>2</sup>, Dobromir Dimitrov<sup>4</sup>, Jeffrey Eaton<sup>2</sup>, Stefan Baral<sup>5</sup>, Deborah Donnell<sup>4</sup>, Marie-Claude Boily<sup>2</sup>, for the Modeling KP and HIV Epidemics Working Group

<sup>1</sup>University of Bristol, Bristol, UK, <sup>2</sup>Imperial College London, London, UK, <sup>3</sup>McGill University, Montreal, Canada, <sup>4</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>5</sup>The Johns Hopkins University, Baltimore, MD, USA

**Background:** Quantifying the contribution of key populations (KP) including female sex workers (FSW), their clients, men who have sex with men (MSM) and young women (15-24 years old) to HIV epidemics due to prevention/treatment gaps is important to plan effective intervention programs. We used mathematical models to compare four different commonly used indicators of the contributions of population subgroups to HIV epidemics.

**Methods:** Fourteen transmission-dynamic mathematical models of HIV, calibrated to different African settings reflecting existing levels of intervention/treatment and existing gaps, were used to derive four indicators for each KP: (1) % incident infections acquired in 2020, (2) % incident infections transmitted in 2020, (3) transmission population attributable fraction (tPAF) over 1-year (2020), (4) tPAF over 10 years (2010-2020). KP-specific correlation plots were used to compare indicators and to assess the level of agreement between indicators on the greatest contributor to HIV.

**670 AGING AND THE HIV EPIDEMIC AMONG MSM IN THE US: A COMPARISON OF 2 SIMULATION MODELS**

Emily P. Hyle<sup>1</sup>, Parastu Kasaie<sup>2</sup>, Eli L. Schwamm<sup>1</sup>, Cameron Stewart<sup>2</sup>, Krishna P. Reddy<sup>1</sup>, Lucas Gerace<sup>2</sup>, Pamela Pei<sup>1</sup>, Elizabeth Humes<sup>2</sup>, Fatma Shebli<sup>1</sup>, Kenneth Freedberg<sup>1</sup>, Rochelle P. Walensky<sup>1</sup>, Kerri N. Althoff<sup>2</sup>

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

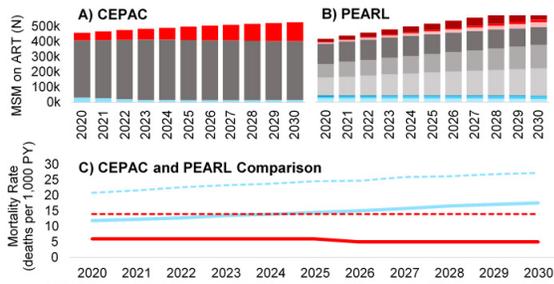
**Background:** With increasing life expectancy, more MSM on ART are likely to survive past 65y and will be at risk for multimorbidity. Using two independent, individual-based models of HIV, we compared projections of the age and number of MSM on ART in the US from 2020 to 2030.

**Methods:** We populated the CEPAC microsimulation model with CDC data to project the HIV epidemic among MSM from 2014 (mean±SD age, 45.2±12.1y), assuming 82% diagnosed, 66% in care and on ART, and 54% virally suppressed. We estimated age-/sex-/CD4-stratified mortality for MSM on/off ART but did not stratify by race. We used model-projected viral load distributions to estimate annual incident HIV cases from 2015-2030 (mean age at infection, 33.4±11.0y), assuming 40% PrEP coverage with 62% adherence after 2016. In the PEARL agent-based simulation of people on ART in the US, we applied observed parameters from NA-ACCORD for the age and CD4-distribution of MSM starting ART, disengagement/reengagement on ART, and mortality on/off ART (all stratified by race/ethnicity). The number of new ART initiators are estimated from CDC-reported HIV diagnoses (calibration, 2010-17). We compared CEPAC and PEARL projections, as well as key assumptions and inputs.

**Results:** Both models projected an aging, growing population of MSM on ART (Figure): CEPAC: mean±SD age, 48.5±12.9y [2020] vs 52.9±13.8y [2030]; PEARL: 46.6±13.0y [2020] vs. 49.4±14.8y [2030]. CEPAC projected 122,200 MSM >65y in 2030 (Panel A), whereas PEARL projected 116,500 MSM aged >65y and underscored that the majority of MSM aged 30-64y in 2030 will be Black or Hispanic (Panel B). We estimated fewer MSM on ART by 2030 in CEPAC than in PEARL due to lower projected engagement in care (Panel C, CEPAC: 76-77%;

PEARL: 93-96%) and higher mortality among MSM on ART. Mortality in CEPAC (on ART, 12.3-18.3/1000PYs; off ART, 21.7-27.8/1000PYs [2020-30]) increased over the decade reflecting the older ages of MSM, while PEARL projected reduced mortality (on ART, 6.5-5.4/1000PYs; off ART, 14.5-14.1/1000PYs [2020-30]) given improved survival rates on ART.

**Conclusion:** We projected substantial aging of MSM on ART in the US over the next decade in both the CEPAC and PEARL models. While each model has simplifying assumptions and different parameterization, this comparison highlights important data gaps and uncertainties. Better estimates of engagement in care, ART usage, and mortality among MSM with HIV will be critical to the study of HIV aging and multimorbidity over the next decade.



**Figure 671: Projected characteristics of US HIV epidemic among MSM, 2020-2030.** CEPAC- and PEARL-projected number of MSM on ART (Panels A and B, respectively) MSM aged <30y - blue; 30-64y - gray; 65y+ - red; PEARL outcomes are additionally stratified by race/ethnicity (Black - light; Hispanic - medium; White - dark). Panel C shows CEPAC- (blue) and PEARL- (red) projected mortality rates among MSM on ART (solid) or off ART (dashed).

**671 CALIBRATION OF THE VACS INDEX 2.0 FOR ESTIMATING MORTALITY AMONG PWH IN NORTH AMERICA**

**Kathleen A. McGinnis<sup>1</sup>, Amy Justice<sup>2</sup>, Richard Moore<sup>3</sup>, Michael J. Silverberg<sup>4</sup>, Keri N. Althoff<sup>3</sup>, Maile Karris<sup>5</sup>, Viviane D. Lima<sup>6</sup>, Heidi Crane<sup>7</sup>, Michael A. Horberg<sup>8</sup>, Marina B. Klein<sup>9</sup>, Stephen Gange<sup>3</sup>, Kelly Gebo<sup>3</sup>, Angel Mayor<sup>10</sup>, Janet P. Tate<sup>1</sup>**, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

<sup>1</sup>VA Connecticut Healthcare System, West Haven, CT, USA, <sup>2</sup>Yale School of Medicine, New Haven, CT, USA, <sup>3</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>4</sup>Kaiser Permanente, Northern CA, Oakland, CA, USA, <sup>5</sup>University of California, San Diego, USA, <sup>6</sup>The University of British Columbia, Vancouver, Canada, <sup>7</sup>University of Washington, Seattle, WA, USA, <sup>8</sup>Mid-Atlantic Permanente Research Institute, Washington, DC, MD, <sup>9</sup>McGill University, Montreal, Canada, <sup>10</sup>Universidad Central del Caribe, Bayamon, PR, USA

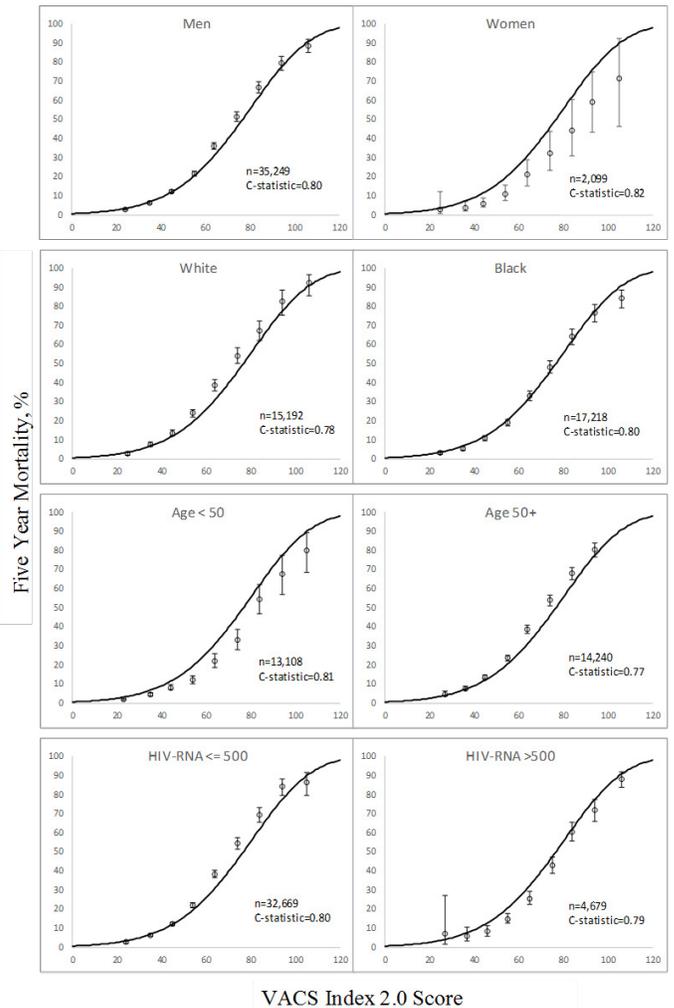
**Background:** The Veterans Aging Cohort Study (VACS) Index 1.0 incorporated general and HIV-specific health biomarkers (age, hemoglobin, FIB-4, eGFR, Hepatitis C virus [HCV], HIV-1 RNA, and CD4) and discriminated mortality risk in persons with HIV (PWH). Conversion from categorical to continuous forms of variables and the addition of BMI, total white blood count, and albumin (VACS Index 2.0) substantially improved discrimination. In preparation for estimating remaining life expectancy, our current aim is to evaluate the calibration of VACS Index 2.0 in the North American AIDS Cohort Collaboration (NA-ACCORD), which comprises over 20 cohorts in the US and Canada, including VACS.

**Methods:** We included VACS and three other NA-ACCORD cohorts that collected the required data elements and ascertained mortality with the National Death Index. Among participants on ART for at least one year, we randomly chose a VACS Index 2.0 at least one year after start of ART as "baseline" (ranging from 10/1999 – 4/2018) to ensure the sample included PWH at different stages of HIV. Five-year mortality was calculated up to 3/2019 or cohort close date. Calibration curves were generated by comparing predicted mortality overall (estimated using a gamma model with the VACS Index Score 2.0 as the only predictor) to observed mortality for the subgroups gender, age50, race, and HIV-1 RNA500 copies/mL at baseline. Observed mortality is based on Kaplan-Meier estimates, and C-statistics were generated to assess discrimination.

**Results:** Of 6,429 PWH in the three NA-ACCORD cohorts and 30,919 in VACS, median age was 46 and 56 years; 20% and 3% were women; 38% and 48% were African-American, 40% and 41% White; and 24% and 22% had a history of HCV, respectively. Median follow-up time was 3.5 years (1.9-5.0). VACS Index 2.0 showed greater discrimination than VACS Index 1.0 overall (0.80 vs. 0.77, p<.001) and for all subgroups. In overall and subgroup analyses, predicted and observed mortality largely overlapped, although was overestimated among women and those less than 50 years.

**Conclusion:** VACS Index 2.0 improves discrimination over VACS Index 1.0 in NA-ACCORD and across a wide range of subgroups. Calibration is good overall although there is overestimation in certain subgroups.

**Figure 672: 5-year mortality by VACS Index 2.0 for important subgroups.** Observed 5-year mortality is shown with 95% confidence intervals. Solid lines reflect predicted mortality calculated using both NA-ACCORD and VACS data



solid line = predicted mortality from gamma model using VACS Index V2 score as the only predictor  
circles = observed 5-year mortality estimated using Kaplan-Meier method, with 95% confidence intervals

**672 PREDICTIVE MODELS OF ART RESPONSES AMONG ACUTELY INFECTED INDIVIDUALS**

**Robert Paul<sup>1</sup>, Andrew Belden<sup>1</sup>, Jintanat Ananworanich<sup>2</sup>, Kyu Cho<sup>1</sup>, Carlo Sacdalan<sup>3</sup>, Eugene Kroon<sup>3</sup>, Lishomwa Ndhlovu<sup>4</sup>, Lydie Trautmann<sup>5</sup>, Somporn Tipsuk<sup>3</sup>, Duanghathai Suttichom<sup>3</sup>, Donn J. Colby<sup>6</sup>, Nittaya Phanuphak<sup>3</sup>, Sandhya Vasan<sup>6</sup>, Serena S. Spudich<sup>7</sup>**, for the SEARCH 010/RV254 Study Team

<sup>1</sup>University of Missouri St Louis, St Louis, MO, USA, <sup>2</sup>Bill & Melinda Gates Medical Research Institute, Bethesda, Maryland, USA, <sup>3</sup>SEARCH, Bangkok, Thailand, <sup>4</sup>Weill Cornell Medicine, New York, NY, USA, <sup>5</sup>Oregon Health and Sciences University, Portland, OR, USA, <sup>6</sup>US Military HIV Research Program, Silver Spring, MD, USA, <sup>7</sup>Yale University, New Haven, CT, USA

**Background:** The present study employed a combination of data science and inferential analytic methods to delineate the early and ongoing risk factors for clinical phenotype variability in a large group of individuals who initiated treatment during acute HIV (AH).

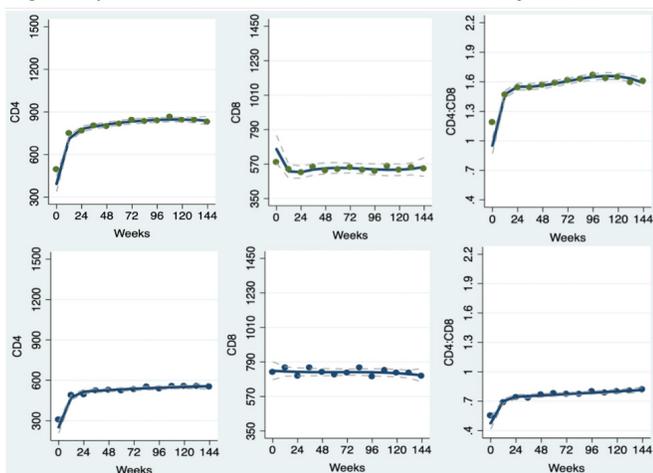
**Methods:** Participants included 412 Thai adults enrolled in RV254/SEARCH 010 who completed longitudinal multi-omic (e.g., viral, immune, neuro, psychosocial) assessments before and after 144 weeks of ART. Individuals were classified into favorable vs. unfavorable clinical phenotypes at weeks 96 and 144 using previously established criteria (CD4 T cell count >500, CD4/CD8 T cell ratio >1.0, and presence of viral blips). Outcomes included phenotype designation, baseline predictors, and risk trajectories modeled through weeks 96 and 144

post ART. Group comparisons and hierarchical clustering examined correlates of trajectory subgroup membership.

**Results:** Participants were mostly male (97%), Fiebig stages I-III (86%), with a CD4 T cell count >350 at baseline and undetectable viral status by week 24. Less than half (40% and 41%) of the study sample achieved a favorable clinical phenotype at weeks 96 and 144, respectively. Baseline CD4/CD8 T cell ratio was the strongest determinant of clinical phenotype designation at both follow-up time points. Older age, increased self-report of depressive symptoms, and increased neutrophil count at baseline contributed to the prediction models. Multivariate trajectory analysis revealed five subgroups of CD4, CD8 and CD4/CD8 ratio profiles (see Figure 1). Two of the subgroups (46% of the sample) exhibited early and chronic CD4/CD8 T cell ratio inversion, owing to either incomplete CD4 T cell recovery (max CD4 <500; 36% of the sample) or persistently increased CD8 T cells in the context of robust CD4 recovery (max CD4 >850). Baseline depressive symptoms, later Fiebig stage at ART onset, and levels of IL-7, IL-23, CD27, Tim-3, and RANTES differentiated the CD4/CD8 T cell ratio trajectory subgroups and clinical phenotype designation at week 144.

**Conclusion:** A combination of psychosocial, viral, and immune factors (including myeloid and lymphocyte T cell populations) at the time of ART onset predict clinical phenotype variability after 144 weeks of treatment. Baseline risk variables differentiate CD4 and CD8 subgroups and chronic CD4/CD8 T cell ratio inversion and clinical phenotype designation.

**Figure 1.** Trajectories of CD4, CD8 and CD4/CD8 T cell ratio from baseline through week 144.



**Fig. 1.** Depiction of CD4 (left), CD8 (middle), and CD4/CD8 T cell ratio (right) trajectories from baseline through week 144 for the two subgroups (top and bottom rows) with CD4/CD8 T cell ratio <1 from baseline through week 144 post ART. CD4/CD8 T cell ratio inversion was explained by poor CD4 T cell recovery in 36% of the sample and chronic elevation of CD8 T cells in 10% of the sample. Individuals in both trajectory subgroups met criteria for the unfavorable clinical phenotype at weeks 96 and 144 despite sustained use of ART and undetectable viral load.

## 673 DEVELOPING A PREDICTIVE MODEL FOR HIV CLINICAL CARE DISENGAGEMENT

**Monica Borges**<sup>1</sup>, Charles Burns<sup>1</sup>, Mehri McKellar<sup>1</sup>, Nwora Lance Okeke<sup>1</sup>  
<sup>1</sup>Duke University, Durham, NC, USA

**Background:** Disengaging from care is associated with all-cause mortality in people living with HIV (PLWH); therefore, tools that can assist with the early identification of persons at-risk for falling out of care are needed. The electronic health record (EHR) serves as an invaluable platform to create such tools. We present an EHR-based predictive model for early identification of persons at high-risk of falling out of HIV care.

**Methods:** We analyzed EHR-data from HIV clinic patients in care at Duke between Jan 2014 and Dec 2018. Clinical data on 38 candidate variables (demographics, sexually transmitted disease (STD) diagnoses, substance abuse, mental health and healthcare utilization patterns) were collected for possible inclusion in the model. The outcome of interest, disengaging from care, was defined as failure to attend an HIV clinic appointment for ≥ 12 months after documentation of clinic encounters prior to the period of absence. LASSO regression was used in selecting features for a logistic model. The model performance criterion used for LASSO was area under the receiver operating characteristic curve (AUC). A non-regularized logistic model was then fit using the LASSO-selected predictors to verify performance on the testing set. AUC

was calculated to assess model performance, and estimated coefficients were transformed to adjusted odds ratios.

**Results:** 2301 subjects (mean age 47 years; 72% male; 58% Black) were included in analysis. Predictor variables positively associated with disengaging from care include number of positive gonorrhea or chlamydia tests; number of recent syphilis tests (OR, 95% CI: 1.38, 1.23-1.56); ever being diagnosed with syphilis; a positive amphetamines test; and schizophrenia diagnosis (OR, 95% CI: 2.83, 1.18-6.78). Predictors negatively associated with disengagement from care are higher age (OR, 95% CI: 0.98, 0.96-0.99); number of recent gonorrhea/chlamydia tests taken (OR, 95% CI: 0.77, 0.73-0.81); 2+ emergency visits; 1+ hospital admissions; 2+ hospital admissions (OR, 95% CI: 0.2, 0.06-0.67); depression diagnosis (OR, 95% CI: 0.63, 0.45-0.87); and visiting the HIV clinic in each half of the year (OR, 95% CI: 0.2, 0.15-0.27). A logistic regression model using these predictors for the testing set results in an AUC of 0.78.

**Conclusion:** A model including demographics, STD diagnoses, mental health diagnosis, and healthcare utilization behavior variables effectively identifies PLWH at-risk for care disengagement.

## 674 PARTNER TESTING AMONG PREGNANT WOMEN OFFERED HIV RETESTING IN KENYA

**Wenwen Jiang**<sup>1</sup>, Peninah Kitao<sup>2</sup>, Shiza Farid<sup>1</sup>, Daniel Matemo<sup>2</sup>, Anjuli Wagner<sup>1</sup>, Cheryl C. Johnson<sup>3</sup>, Grace John-Stewart<sup>1</sup>, John Kinuthia<sup>2</sup>, Alison L. Drake<sup>1</sup>, David Katz<sup>1</sup>

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Kenyatta National Hospital, Nairobi, Kenya, <sup>3</sup>World Health Organization, Geneva, Switzerland

**Background:** Near-universal HIV testing among pregnant women through maternal and child health (MCH) services provides opportunities to reach male partners for HIV testing, yet partner testing remains low. In trials, secondary distribution of HIV self-tests by pregnant women has increased partner testing, but there is limited real-world evidence on partner testing when self- and clinic testing are options.

**Methods:** At 3 Kenyan MCH clinics, we offered HIV-negative pregnant women a choice of standard clinic-based testing (CBT) or HIV self-testing at home (HBT) for HIV retesting for themselves. Women who selected HBT were offered additional self-test kits for male partner testing; while women who selected CBT could refer partners to clinic for routine testing. We assessed HIV testing uptake among male partners by 14 weeks postpartum. We used generalized linear mixed regression with Poisson distribution to (1) identify correlates of partner testing, stratified by whether women selected HBT or CBT, and (2) and partner testing via HBT (vs. CBT) among women selecting HBT.

**Results:** Among 798 women, median age was 24 years and most were cohabiting with partners (87%). By 14 weeks postpartum, 163 (60%) of 270 women who selected HBT for themselves at enrollment and 200 (38%) of 528 of women who selected CBT reported partner HIV testing (p<0.001). Of those reporting partner testing, 314 (87%) reported partner status negative, 2 positive, and 47 did not report results. Among all women (both HBT and CBT), partner testing was associated with higher maternal education and cohabiting in multivariate analyses. Additionally, among women selecting CBT, partner testing was associated with having partner >5 years older and not reporting low sexual relationship power (Table 1). In a subset of 163 women opting for HBT whose partners tested, 64% reported partners tested via HBT, 33% via CBT and 3% were missing test method. Partner testing via HBT rather than CBT was associated with higher household income (≥10,000 KSH) (prevalence ratio 1.51, 1.35-1.70), but this was not significant in the adjusted model (not shown in table).

**Conclusion:** Offering secondary distribution of HIV self-testing to male partners of women receiving HIV services at MCH clinics can increase partner testing coverage and maximize HIV prevention efforts. Understanding barriers and facilitators to women's delivery of self-tests to partners and partner self-testing could inform targeted approaches to further improve partner testing within MCH services.

**Table 1. Characteristics associated with male partner HIV testing, stratified by women who selected home-based (HBT) vs. clinic-based testing (CBT) at enrollment (N=798)**

|   | Women selecting HBT at enrollment (N=270) |                                  | Women selecting CBT at enrollment (N=528) |                                  |
|---|---|----------------------------------|---|----------------------------------|
|   | Crude PR <sup>a</sup> (95%CI)             | Adjusted PR <sup>a</sup> (95%CI) | Crude PR (95%CI)                          | Adjusted PR <sup>a</sup> (95%CI) |
| Western Kenya (ref: Nairobi)                      | 1.02 (0.84-1.24)                          | 1.11 (0.92-1.35)                 | 0.81 (0.65-1.01)*                         | 0.94 (0.73-1.19)                 |
| Age (years)                                       | 0.99 (0.97-1.02)                          |                                  | 0.99 (0.96-1.01)                          |                                  |
| Years of completed education                      | 1.05 (1.01-1.08)**                        | 1.05 (1.02-1.09)**               | 1.04 (1.01-1.08)**                        | 1.04 (1.00-1.08)**               |
| Monthly household income ≥10,000 KSH (~\$100 USD) | 1.02 (0.84-1.25)                          |                                  | 1.35 (1.07-1.69)**                        | 1.15 (0.91-1.47)                 |
| Have any living children                          | 0.99 (0.82-1.19)                          |                                  | 0.83 (0.67-1.03)*                         | 0.88 (0.70-1.12)                 |
| Current pregnancy intended                        | 0.94 (0.77-1.14)                          |                                  | 1.29 (1.01-1.64)**                        | 1.25 (0.96-1.62)*                |
| Partner age difference >5 years                   | 0.96 (0.79-1.17)                          |                                  | 1.36 (1.10-1.70)**                        | 1.39 (1.11-1.73)**               |
| Living with partner                               | 1.44 (0.94-2.22)*                         | 1.56 (1.02-2.39)**               | 1.36 (0.94-1.97)*                         | 1.64 (1.05-2.57)**               |
| Low sexual relationship power <sup>b</sup>        | 1.06 (0.87-1.31)                          |                                  | 0.66 (0.49-0.89)**                        | 0.71 (0.51-0.98)**               |
| Partner ever tested for HIV in past               | 0.98 (0.79-1.21)                          |                                  | 1.18 (0.90-1.55)                          |                                  |

Note: \*PR: Prevalence Ratio; <sup>b</sup>Score in lowest quantile (<2.13) on Sexual Relationship Power Scale (SRPS)

\*p-value <0.1

\*\*p-value <0.05

# adjusted model includes study site and covariates with \*p-value <0.1

## 675 INNOVATIVE QUALITY APPROACH TO IMPROVE HIV RAPID TESTING IN SOUTH AFRICA

**Karidia Diallo**<sup>1</sup>, Mireille B. Kalou<sup>2</sup>, Makhanya Makhosazana<sup>1</sup>, Adeboye Adelekan<sup>1</sup>, Leigh Berrie<sup>1</sup>, Kemba N. Lee<sup>3</sup>, Kassahun Ayalew<sup>1</sup>, Joseph Honwani<sup>4</sup>, Dumisani Mhlongo<sup>5</sup>, Robert Molale<sup>5</sup>, Anil Kalan<sup>6</sup>, Amanda Mohlale<sup>6</sup>, Bandile Ndaziz<sup>6</sup>, Peter Manyike<sup>6</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Pretoria, South Africa, <sup>2</sup>Centers for Disease Control and Prevention, Port-Au-Prince, Haiti, <sup>3</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>4</sup>National Department of Health, Pretoria, South Africa, <sup>5</sup>National Health Laboratory Service, Johannesburg, South Africa, <sup>6</sup>Strategic Evaluation, Advisory & Development Consulting (Pty) Ltd, Cape Town, South Africa

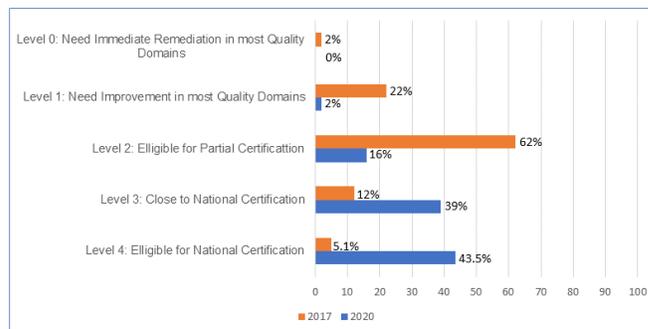
**Background:** In 2014, South Africa piloted the Rapid Test Continuous Quality Improvement (RTCQI) initiative to improve HIV testing at 2,077 facilities. Preliminary data showed some improvement in pre-testing, testing, and post-testing phases, which ultimately affect the accuracy of diagnosis. To address the gaps identified during the pilot phase and improve accuracy of test results, RTCQI was implemented in 2,600 US President's Emergency Plan for AIDS Relief (PEPFAR)-supported facilities. We report improvement achieved in a cohort of 690 randomly selected facilities.

**Methods:** The Stepwise Process for Improving the Quality of HIV Rapid Testing (SPI-RT) checklist, was used to assess the annual improvement in pre-defined quality standards for HIV rapid testing, including pre-testing, testing, and post-testing. Assessment results were converted to percentages, and facilities were rated (levels 0–4). Level 0 indicates improvement needed in all quality standard domains, whereas level 4 indicates readiness for national certification. Facilities' improvement after implementing RTCQI was determined using McNemar's test, and pre- and post- test improvements were compared using paired t-test

**Results:** A cohort of 690 (26.5%) facilities, with a complete dataset from 2017 to 2020, showed improvements in pre-testing, testing, and post-testing domains. The proportion of level 4 facilities increased from 5.1% (95% CI, 3.6%–7.0%) in 2017 to 43.5% (95% CI, 40.0%–47.3%) in 2020 (p-value <0.0001), whereas the proportion of level 1 facilities that needed improvement in some domains significantly decreased from 22.0% in 2017 to 2.0% in 2020 (Figure). The average performance score of the facilities at Level 4 for the pre-testing, testing and post-testing domains increased by 6.6% (95% CI, 5.6%–7.6%), 11.2% (95% CI, 9.6–12.7) and 5.7% (95% CI, 4.7%–6.7%) respectively by 2020. Qualitative assessment of the data showed improvement in activities implemented directly by the providers, such as enhanced stock and consumables management, increased uptake of internal quality control measures and HIV-testing registers, and proper documentation of test results in the registers.

**Conclusion:** We found significant improvement in quality standards in facilities offering HIV RT that implemented the RTCQI. These improvements were due to monitoring HIV-testing quality standards as part of the HIV Testing Services' policy and allocating human resources at the provincial level to oversee the implementation of and adherence to these standards

Figure: Distribution of the South African facilities (n=690) implementing Rapid Test Continuous Quality Improvement by level of performance (2017–2020)



## 676 HIV RAPID TESTING AND CARE OUTCOMES IN ENDING THE HIV EPIDEMIC JURISDICTIONS

**Anne H. Peruski**<sup>1</sup>, Nivedha Panneer<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** The U.S. Ending the HIV Epidemic (EHE) initiative includes diagnosis and treatment as two of its four pillars. Efforts will initially be focused in EHE priority jurisdictions. Understanding the relationship between diagnosis methods and care outcomes is important when assessing optimal testing strategies. Here we determined care outcomes for persons whose HIV was identified using rapid testing algorithms and all other diagnostic methods in EHE priority jurisdictions as well as all other jurisdictions.

**Methods:** We used data reported to the U.S. National HIV Surveillance System by December 2019 for persons with HIV diagnosed during 2018. Rapid testing algorithms were defined as 1) two consecutive positive CLIA-waived rapid immunoassays conducted on the same date or 2) a positive CLIA-waived rapid immunoassay followed by any positive HIV test within 30 days. We calculated linkage to care ( $\geq 1$  CD4+ or viral load test) and viral suppression ( $< 200$  cp/ml) within 1 and 6 months of diagnosis respectively, for diagnoses made with rapid versus other methods in EHE priority and all other jurisdictions.

**Results:** Among 37,864 persons with HIV diagnosed during 2018, 1,867 (4.9%) were identified using a rapid testing algorithm. The distribution was the same for the 1,086 persons who resided in EHE priority jurisdictions (4.9%) and the 781 persons in all other jurisdictions (4.9%). More persons whose HIV was diagnosed using a rapid testing algorithm were linked to care within one month compared with persons whose HIV was diagnosed using other diagnostic methods (84.5% and 80.0%, respectively), and more persons whose HIV was diagnosed using a rapid testing algorithm achieved viral suppression within 6 months, compared with persons whose HIV was diagnosed using other diagnostic methods (70.4% and 66.6%).

**Conclusion:** Persons with HIV diagnosed using a rapid testing algorithm have better care outcomes as measured by linkage to care and viral suppression. Improved linkage and viral suppression might result from improved turnaround times for rapid test results, which might result in lower loss to follow up. Increasing the number of facilities, including non-clinical facilities, that offer rapid tests, especially in EHE priority jurisdictions, may lead to better health outcomes and less onward transmission.

## 677 HIV SELF-TESTING AND RISK BEHAVIORS AMONG MEN WHO HAVE SEX WITH MEN IN 23 US CITIES

**Cedric Bien-Gund**<sup>1</sup>, Pamela A. Shaw<sup>1</sup>, Christine Agnew Brune<sup>2</sup>, Kathleen Brady<sup>3</sup>, Robert Gross<sup>1</sup>

<sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>3</sup>Philadelphia Department of Public Health, Philadelphia, PA, USA

**Background:** HIV self-testing (HIVST), whereby individuals conduct and interpret their own tests, is a promising strategy to expand the HIV care continuum. However, little is known about uptake among men who have sex with men (MSM), a priority population with high HIV incidence. There is concern that HIVST may increase risk behaviors if individuals test negative. We assessed factors associated with HIV self-testing, and whether self-testing was associated with preventive behaviors among MSM in the US.

**Methods:** We analyzed data from the 2017 CDC National HIV Behavioral Surveillance (NHBS) system, which collected data on HIV risk behaviors, prevention services, and offered HIV testing to MSM through venue-based sampling (VBS) across 23 US cities. We restricted our analysis to MSM who reported HIV-negative or unknown status and obtained HIV testing within the past year. Our primary outcome was HIVST at least once in the past year. We used Poisson regression with a robust variance estimator to calculate adjusted prevalence rate ratios of factors associated with HIVST. Multivariable models were adjusted for age, race/ethnicity, city, and VBS recruitment event.

**Results:** Of 10,760 total participants, 6,563 reported HIV-negative/unknown status and testing in the previous year and were included. 506 (7.7%) individuals reported HIVST in the past year, one of whom reported seroconverting, and 10 of whom were subsequently diagnosed with HIV during the survey. HIVST was associated with younger age, higher education, and higher income (Table). HIVST was also associated with sexual orientation disclosure, having >8 male partners in the past year, more frequent HIV testing, having a more recent HIV test, and discussing HIV prevention strategies with an outreach worker. We did not observe an association with having newly diagnosed HIV, PrEP awareness, PrEP use, condomless anal sex, or STIs in the past year.

**Conclusion:** HIVST was associated with increased test frequency without a significant increase in HIV risk behaviors such as condomless anal sex, STIs, or a new HIV diagnosis. Interventions may be warranted to increase HIVST and linkage to other prevention measures such as PrEP, particularly among MSM with lower income and education to improve awareness of HIV status.

Table: HIV Self-Testing among men who have sex with men reporting HIV-negative or unknown status in the National HIV Behavioral Surveillance System—23 US cities, 2017

| Characteristic                                | Total N (N=6,563 <sup>1</sup> ) | HIV self-testing N = 506 (8%) | Adjusted PR <sup>2</sup> (95% CI) | P-value |
|---|---------------------------------|-------------------------------|-----------------------------------|---------|
| Age   |                                 |                               |                                   |         |
| 18-24   | 1,177                           | 97 (8%)                       | 4.40 (2.16-8.95)                  | <0.001  |
| 25-34   | 2,939                           | 274 (9%)                      | 4.99 (2.50-9.93)                  | <0.001  |
| 35-44   | 1,236                           | 84(7%)                        | 3.62 (1.80-7.32)                  | <0.001  |
| 45-54   | 794                             | 43(5%)                        | 2.78 (1.32-5.82)                  | 0.001   |
| 55+   | 417                             | 8 (2%)                        | Ref                               |         |
| Race/Ethnicity                                |                                 |                               |                                   |         |
| Black   | 1,812                           | 131 (7%)                      | Ref                               |         |
| Hispanic/Latino                               | 1,722                           | 137 (8%)                      | 1.11 (0.88-1.41)                  | 0.38    |
| White   | 2,401                           | 192 (8%)                      | 1.21 (0.98-1.52)                  | 0.08    |
| Other   | 588                             | 42 (7%)                       | 0.99 (0.71-1.39)                  | 0.98    |
| Income  |                                 |                               |                                   |         |
| \$0 - \$12,499                                | 889                             | 47 (5%)                       | Ref                               |         |
| \$12,500-\$24,999                             | 228                             | 9 (4%)                        | 0.74 (0.39-1.42)                  | 0.37    |
| \$25,000 - \$49,999                           | 2,472                           | 194 (8%)                      | 1.35 (1.00-1.81)                  | 0.05    |
| \$50,000 - \$74,999                           | 1,224                           | 96 (8%)                       | 1.42 (1.02-1.97)                  | 0.04    |
| >\$75,000                                     | 1,698                           | 157 (9%)                      | 1.82 (1.31-2.52)                  | <0.001  |
| Education                                     |                                 |                               |                                   |         |
| High school or less                           | 1,325                           | 83 (6%)                       | Ref                               |         |
| Some college                                  | 2,132                           | 156 (7%)                      | 1.10 (0.85-1.44)                  | 0.47    |
| Completed college                             | 2,055                           | 164 (8%)                      | 1.28 (0.97-1.68)                  | 0.08    |
| More than college                             | 1,047                           | 103 (10%)                     | 1.73 (1.28-2.35)                  | <0.001  |
| Sexual orientation disclosure                 |                                 |                               |                                   |         |
| No  | 253                             | 7 (3%)                        | Ref                               |         |
| Yes   | 6,308                           | 499 (8%)                      | 2.28 (1.10-4.74)                  | 0.03    |
| # of tests in past two years                  |                                 |                               |                                   |         |
| 1-2   | 1,966                           | 117 (6%)                      | Ref                               |         |
| 3-5   | 2,544                           | 208 (8%)                      | 1.33 (1.07-1.64)                  | 0.01    |
| 6-8   | 1,359                           | 129 (9%)                      | 1.50 (1.17-1.91)                  | 0.001   |
| 9 or more                                     | 561                             | 52 (9%)                       | 1.43 (1.04-1.97)                  | 0.03    |
| Time of last HIV test                         |                                 |                               |                                   |         |
| 7-12 months ago                               | 1,344                           | 77 (6%)                       | Ref                               |         |
| 4-6 months ago                                | 1,426                           | 112 (8%)                      | 1.28 (0.96-1.71)                  | 0.09    |
| <3 months                                     | 3,638                           | 314 (9%)                      | 1.39 (1.08-1.78)                  | 0.01    |
| Discussed HIV prevention with outreach worker |                                 |                               |                                   |         |
| No  | 4,076                           | 291 (7%)                      | Ref                               |         |
| Yes   | 1,979                           | 215 (10%)                     | 1.40 (1.18-1.67)                  | <0.001  |
| # Male sex partners, 12 months                |                                 |                               |                                   |         |
| 0-1   | 1,220                           | 69 (6%)                       | Ref                               |         |
| 2-4   | 1,864                           | 137 (7%)                      | 1.16 (0.87-1.55)                  | 0.31    |
| 5-7   | 1,030                           | 83 (8%)                       | 1.25 (0.90-1.72)                  | 0.18    |
| 8 or more                                     | 2,421                           | 211 (9%)                      | 1.37 (1.03-1.82)                  | 0.03    |

<sup>1</sup>Total number of responses may not add to 6,563 due to missing data.

<sup>2</sup>Prevalence rate ratio (PR) estimated from separate Poisson regression models adjusted for age, race/ethnicity, and city, and clustered on VBS recruitment event.

678 **USE OF MULTI-ASSAY ALGORITHMS TO IDENTIFY RECENT HIV INFECTIONS: HPTN 071/POPART**

**Wendy Grant-McAuley<sup>1</sup>**, Ethan Klock<sup>1</sup>, Oliver Laeyendecker<sup>1</sup>, Yaw Agyei<sup>1</sup>, Ethan A. Wilson<sup>2</sup>, William Clarke<sup>1</sup>, Autumn Breaud<sup>1</sup>, Ayana Moore<sup>3</sup>, Helen Ayles<sup>4</sup>, Peter Bock<sup>5</sup>, Deborah Donnell<sup>2</sup>, Sarah Fidler<sup>6</sup>, Richard Hayes<sup>7</sup>, Susan Eshleman<sup>1</sup>, for the HPTN 071 (PopART) Study Team

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>FHI 360, Durham, NC, USA, <sup>4</sup>Zambart, Lusaka, Zambia, <sup>5</sup>Desmond Tutu TB Centre, Western Cape, South Africa, <sup>6</sup>Imperial College London, London, UK, <sup>7</sup>London School of Hygiene & Tropical Medicine, London, UK

**Background:** Multi-assay algorithms (MAAs) developed for estimating HIV incidence from population-level surveys have also been used to identify individuals with recent infection. Little is known about the performance of these methods for individual-level recency assessments. The most widely used MAA for incidence estimation includes the limiting antigen avidity assay (LAG-Avidity) plus HIV viral load (CDC MAA). We compared the performance of the CDC MAA to three other MAAs for identifying persons infected <1 year as recently infected.

**Methods:** This study included samples from 220 seroconverters (infected <1 year) and 4,396 non-seroconverters (infected >1 year) enrolled in an HIV prevention trial in Zambia and South Africa; 28.6% of seroconverters and 73.4% of non-seroconverters were virally suppressed at sample collection (viral load ≤400 copies/mL). Samples were tested using two laboratory-based assays (LAG-Avidity, BioRad-Avidity) and a point-of-care assay (Assanté HIV-1 Rapid Recency assay; rapid LAG). Four MAAs were evaluated that included different combinations of assays with different assay cutoffs (Table).

**Results:** The four MAAs classified different numbers of seroconverters (54 [24.5%] to 100 [45.5%]) and non-seroconverters (11 [0.3%] to 69 [1.6%]) as recently-infected. Sensitivity, specificity, and the false recent rate for identifying seroconverters as recent varied among the MAAs (Table). Two MAAs classified fewer seroconverters as recent than expected based on their mean window periods (CDC MAA, p=0.0004; Clade C MAA, p <0.0001). The 60 seroconverters classified as recent by the CDC MAA were a subset of the 100 seroconverters classified as recent by the Clade C MAA. Seventy-two seroconverters were classified as recent by the CDC MAA and/or the Rapid LAG MAA; these MAAs use different LAG assays with the same viral load cutoff. These 72 seroconverters included 12 classified as recent by the Rapid LAG MAA only, 18 identified as recent by the CDC MAA only, and 42 classified as recent by both MAAs.

**Conclusion:** Substantial differences were observed in the performance of four MAAs for identifying individuals infected <1 year as recently infected. Each MAA classified different groups of individuals as recent vs. non-recent, even when the MAAs differed only in the type of LAG assay used (lab-based assay vs. rapid). These performance issues should be considered when using these MAAs for applications designed to identify individuals with recent HIV infection.

Table. Performance of MAAs for classifying persons infected <1 year as recently infected.

|                                       | CDC MAA | Clade C MAA | Rapid LAG MAA | Alternate MAA |
|---------------------------------------|---------|-------------|---------------|---------------|
| <b>Seroconverters (N=220)</b>         |         |             |               |               |
| True recent                           | 60      | 100         | 54            | 81            |
| False non-recent                      | 160     | 120         | 166           | 139           |
| <b>Non-seroconverters (N=4,396)</b>   |         |             |               |               |
| True non-recent                       | 4,385   | 4,362       | 4,379         | 4,336         |
| False recent                          | 11      | 34          | 17            | 69            |
| Sensitivity                           | 27.3%   | 45.5%       | 24.5%         | 36.8%         |
| Specificity                           | 99.7%   | 99.2%       | 99.6%         | 98.4%         |
| Positive predictive value             | 84.5%   | 74.6%       | 76.1%         | 54.0%         |
| Negative predictive value             | 96.5%   | 97.3%       | 96.3%         | 96.9%         |
| False recent rate (infected >2 years) | 0.2%    | 0.5%        | 0.4%          | 1.3%          |
| Window period (days)                  | 142     | 248         | 105           | 126           |
| Expected recent                       | 86      | 149         | 63            | 76            |

CDC MAA: LAG<1.5 + VL>1000; Clade C MAA: LAG<2.8 + BioRad AI <95 +VL >400; Rapid LAG MAA: Rapid LAG recent + VL>1000; Alternate MAA: LAG<2.8 + BioRad AI <40.

## 679 HIV REGENCY TESTING, A TOOL FOR HIV HOT SPOT MAPPING: CRS EpiC3-90 EXPERIENCE, ZAMBIA

Linda Mwila Chibesa<sup>1</sup>, Albert Mwangi<sup>1</sup>, Towela N. Mfune<sup>1</sup>, Sabe Mwape<sup>1</sup>, Mwate J. Chaila<sup>1</sup>, Bosco Mukanyimi<sup>1</sup>, Dailes Nsofwa<sup>2</sup>, Keith Mweebo<sup>2</sup>, Elyssa Stoops<sup>2</sup>, Peter Minchella<sup>2</sup>, Samuel Yingst<sup>2</sup>, Aaron Shibemba<sup>3</sup>, Fails Mwamba Zulu<sup>3</sup>, Mwayabo J. Kazadi<sup>1</sup>

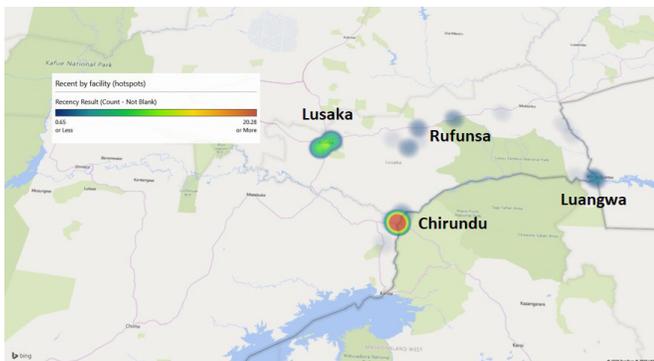
<sup>1</sup>Catholic Relief Services, Zambia, Lusaka, Zambia, <sup>2</sup>Centers for Disease Control and Prevention, Lusaka, Zambia, <sup>3</sup>Ministry of Health, Zambia, Lusaka, Zambia

**Background:** The Epidemic Control 90-90-90 (EpiC 3-90) Project is a U.S Centers for Disease Control & Prevention (CDC) funded project that supports the Ministry of Health (MOH) in Zambia to achieve the UNAIDS 90-90-90 targets in faith-based and government facilities. The scope of support is in four provinces of Zambia, including Lusaka Province, where phase 1 of the HIV recent infection surveillance program was implemented (phase 1 was implemented in Lusaka and Copperbelt provinces). EpiC 3-90 implemented this program in Lusaka Province at 62 supported facilities. Recent infection surveillance aims to establish HIV recent infection status among newly diagnosed HIV positive patients using the HIV-1 recent infection testing algorithm (RITA), which couples the Rapid test for Recent infection (RTRI) with HIV viral load (VL) testing to identify true HIV recent patients (infected within 12 months). The overall aim of the surveillance program is to improve targeted HIV preventive and treatment interventions.

**Methods:** Newly diagnosed HIV positive adults were recruited into the study and all procedures for documentation, consent, and record keeping were upheld. The RTRI was conducted at the hub laboratories, with each of the RTRI recent results subjected to an HIV VL at the PCR labs to determine true recent patients. Data obtained were mapped to districts, facilities, and HIV testing modalities to focus HIV preventive and treatment interventions. EpiC3-90 used this information to strategize on targeted HIV prevention and treatment activities. Findings presented are from November 2019 to September 2020.

**Results:** Out of the patients who were subjected to the RITA, 6.2% (41 unsuppressed VL out of 663 RTRI) were true HIV recent, with young women 20-24yrs leading at 32% (13 out of 41 patients). Chirundu district had a high number of recent infections relative to other districts (Figure 1), at 53.7% (22 out of 41 true recent results came from this district). In addition, Voluntary Counselling and Testing (VCT) modality had the highest percentage of HIV recent patients at 36.4% (8 out of 22 patients).

**Conclusion:** HIV recent infection surveillance is an intervention that can be employed in epidemic control. Recent infection surveillance data suggested that Chirundu, a Zambian border town with Zimbabwe, may be a hot spot district where CRS EpiC 3-90, MOH and other stakeholders should prioritize for HIV preventive and treatment interventions.



## 680 EVALUATION OF A RAPID TEST ALGORITHM TO ESTIMATE HIV INCIDENCE: HPTN 071/PopART

Ethan Klock<sup>1</sup>, Ethan A. Wilson<sup>2</sup>, Reinaldo Fernandez<sup>1</sup>, Denni Lennon<sup>1</sup>, Ayana Moore<sup>3</sup>, Barry Kosloff<sup>4</sup>, Anneen Van Deventer<sup>5</sup>, Helen Ayles<sup>6</sup>, Peter Bock<sup>5</sup>, Deborah Donnell<sup>3</sup>, Sarah Fidler<sup>6</sup>, Richard Hayes<sup>7</sup>, Susan Eshleman<sup>1</sup>, Oliver Laeyendecker<sup>1</sup>, for the HPTN 071 (PopART) Study Team

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>FHI 360, Durham, NC, USA, <sup>4</sup>Zambart, Lusaka, Zambia, <sup>5</sup>Stellenbosch University, Cape Town, South Africa, <sup>6</sup>Imperial College London, London, UK, <sup>7</sup>London School of Hygiene & Tropical Medicine, London, UK

**Background:** Lateral flow point-of-care tests have been designed to identify individuals with recent HIV infection. Use of these assays in algorithms to estimate HIV incidence is not well documented. We evaluated the performance of the Asante HIV-1 Rapid Recency Assay (Rapid) for HIV incidence estimation and compared its performance to the HIV-1 LAg-Avidity EIA (LAg).

**Methods:** HIV incidence was assessed in the community-randomized HPTN 071 (PopART) trial, conducted in South Africa and Zambia. Incidence was estimated cross-sectionally at the 24-month study visit for all participants who had 12-month and 24-month study visits. The resulting estimate was compared to incidence observed longitudinally between those time points. The cohort included 15,845 individuals who tested HIV negative at both visits, 4,406 who tested HIV positive at both visits, and 221 individuals who seroconverted between the study visits. The cross-sectional incidence estimate was determined using the manufacturer's protocol for each assay. For both assays, samples were required to have a viral load (VL) >1000 copies/mL to be considered recent. The mean duration of recent infection (MDRI) was 180 and 130 days for the Rapid+VL and LAg+VL algorithm, respectively. Cross-sectional incidence estimates and 95% confidence intervals (95% CI) were estimated using the ABIE v3 Incidence Calculator. Sub-analyses were performed by country, study arm, sex, and sex among younger participants.

**Results:** Seventy-two participants were classified as recent using the Rapid+VL algorithm: 24% (53/221) of the seroconverters and 0.4% (14/3500) of those known to be infected >2 years. The overall incidence for the Rapid+VL algorithm was 46% lower than observed incidence (Table). In sub-analyses using the Rapid+VL algorithm, incidence estimates were on average 42% lower than observed HIV incidence. In contrast, the overall incidence estimate for the LAg+VL algorithm was 4% lower than observed incidence.

**Conclusion:** The Rapid+VL testing algorithm underestimated HIV incidence in a large population cohort from South Africa and Zambia. This suggests that the MDRI recommended by the manufacturer is too long or that the assay is not accurately detecting a sufficient portion of the recent infections. Additional studies are needed to determine the correct MDRI for this cross-sectional incidence algorithm.

**Table: Comparison of Incidence Algorithms for HIV Incidence Estimation**

| Analysis        | Incidence (per 100 person years) |                   |                   |
|-----------------|----------------------------------|-------------------|-------------------|
|                 | Observed (95% CI)                | Rapid+VL (95% CI) | LAg+VL (95%CI)    |
| All             | 1.34 (1.17, 1.53)                | 0.92 (0.69, 1.15) | 1.29 (0.97, 1.62) |
| Study Arm       |                                  |                   |                   |
| A               | 1.42 (1.15, 1.82)                | 0.62 (0.31, 0.93) | 1.18 (0.68, 1.69) |
| B               | 0.97 (0.74, 1.25)                | 0.72 (0.40, 1.04) | 1.04 (0.60, 1.49) |
| C               | 1.76 (1.41, 2.18)                | 1.51 (0.99, 2.03) | 1.73 (1.08, 2.38) |
| Country         |                                  |                   |                   |
| South Africa    | 1.23 (1.02, 1.56)                | 0.80 (0.49, 1.11) | 1.19 (0.74, 1.64) |
| Zambia          | 1.41 (1.18, 1.67)                | 1.01 (0.70, 1.33) | 1.37 (0.95, 1.80) |
| Sex             |                                  |                   |                   |
| Female          | 1.65 (1.42, 1.90)                | 0.95 (0.68, 1.23) | 1.57 (1.15, 1.99) |
| Male            | 0.64 (0.44, 0.93)                | 0.86 (0.47, 1.24) | 0.65 (0.26, 1.04) |
| 18-24 year olds |                                  |                   |                   |
| Female          | 2.14 (1.69, 2.67)                | 1.30 (0.74, 1.86) | 1.71 (0.96, 2.47) |
| Male            | 0.57 (0.28, 1.02)                | 0.64 (0.12, 1.16) | 0.30 (0.00, 0.71) |

## 681 COMPARISON OF ASANTE AND SWIFT HIV RAPID REGENCY OF INFECTION ASSAYS

Haley Schmidt<sup>1</sup>, Reinaldo Fernandez<sup>1</sup>, Eshan U. Patel<sup>2</sup>, Charles Morrison<sup>3</sup>, Ronald Galiwango<sup>4</sup>, Joseph Kagaayi<sup>4</sup>, M. Kate Grabowski<sup>1</sup>, Aaron Tobian<sup>1</sup>, Andrew Redd<sup>5</sup>, Thomas Quinn<sup>5</sup>, Oliver Laeyendecker<sup>5</sup>

<sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>3</sup>Behavioral, Epidemiologic and Clinical Sciences, FHI, Durham, NC, USA, <sup>4</sup>Rakai Health Sciences Program, Kalisizo, Uganda, <sup>5</sup>National Institutes of Health, Bethesda, MD, USA

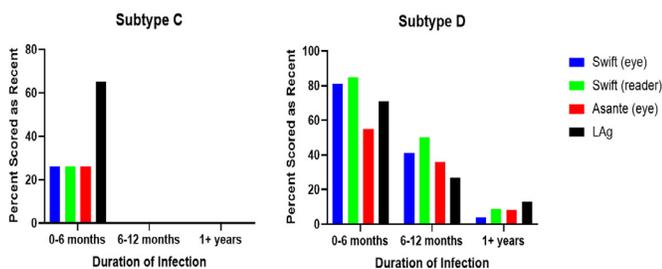
**Background:** Lateral flow point-of-care tests (POCTs) designed to distinguish between recent and long-term HIV-1 infections could increase the feasibility of monitoring population-level HIV transmission in real-time; however, their performance has not been well characterized. We evaluated the performance of the Swift Recent Infection Assay (Swift) and the Asante HIV-1 Rapid Recency Assay (Asante) in a panel of specimens with known duration of infection, and compared their results to the LAg-Avidity EIA (LAg).

**Methods:** Assay performance was evaluated using 254 samples from 141 HIV-positive subjects. This included 26 subjects, half infected with subtype C and half with subtype D (48 samples from <6 months, 48 samples from 6 to 12 months, 43 samples >1 year after seroconversion). An additional 115 samples were from long-term infected subjects (3 to 17 years) from Rakai, Uganda. Assays were conducted per manufacturer protocol. Swift bands were read visually and with the manufacturer's digital reader, while Asante bands were read visually. The lack of a long-term band and viral load >1000 copies/mL were necessary for the classification of recent infection. Cohen's kappa statistics ( $k$ ) were used to assess assay agreement.

**Results:** There was differential classification for recent infection by subtype for both POCTs, which was not seen for LAg ( $n=139$ ) (Figure). Samples from individuals infected with subtype C were correctly classified as recent less frequently than individuals infected with subtype D in the first 6 months (27% vs 85%) or at 6 to 12 months post seroconversion (0% vs 40%). Among long-term infected individuals (>1 years) there was little difference seen between subtypes. For the Rakai samples ( $n=115$ ), ~4% were misclassified by each POCT method. Overall for the Swift ( $n=254$ ), results generated by visual assessment and the digital reader, had high agreement (96%;  $k=0.85$ ). Agreement between visual Swift and LAg was 83% ( $k=0.50$ ), while agreement between digital reader Swift and LAg was 81% ( $k=0.45$ ). Agreement between visual Swift and Asante was 92% ( $k=0.73$ ). The agreement between Asante and LAg was 83% ( $k=0.52$ ). Of note, the lowest agreement between POCTs and LAg was seen in long-term Rakai samples (78%,  $k=0.17$ ).

**Conclusion:** Differential classification of recent infection occurred by subtype for both POCTs. Agreement between visual and digital reader classification for the Swift was high. The classifications of POCTs to LAg were similar, though lowest seen in long-term samples from Rakai.

Percentage Positive by Duration of Infection



## 682 IMPACT OF EARLY VIRAL SUPPRESSION ON HIV INCIDENCE ASSAYS: HPTN 071 (PopART)

Wendy Grant-McAuley<sup>1</sup>, Ethan Klock<sup>1</sup>, Oliver Laeyendecker<sup>1</sup>, Estelle M.

Piwowar-Manning<sup>1</sup>, Ethan A. Wilson<sup>2</sup>, William Clarke<sup>1</sup>, Autumn Breaud<sup>1</sup>, Ayana Moore<sup>3</sup>, Helen Ayles<sup>4</sup>, Peter Bock<sup>5</sup>, Deborah Donnell<sup>2</sup>, Sarah Fidler<sup>6</sup>, Richard Hayes<sup>7</sup>, Susan Eshleman<sup>1</sup>, for the HPTN 071 (PopART) Study Team

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>FHI 360, Durham, NC, USA, <sup>4</sup>Zambart, Lusaka, Zambia, <sup>5</sup>Desmond Tutu TB Centre, Western Cape, South Africa, <sup>6</sup>Imperial College London, London, UK, <sup>7</sup>London School of Hygiene & Tropical Medicine, London, UK

**Background:** Serologic assays used for cross-sectional HIV incidence estimation measure general characteristics of the HIV antibody response. Viral suppression is known to impact the performance of these assays in persons with established infection. Frequent HIV testing and universal antiretroviral treatment (ART) helps many individuals achieve viral suppression in the first year of infection. Little is known about the impact of early viral suppression on the performance of these assays. We evaluated the performance of incidence assays using seroconverter samples from a community-randomized trial that evaluated the impact of universal testing and treatment on HIV incidence (HPTN 071 [PopART]).

**Methods:** This study included samples from 219 study participants who were infected <1 year (seroconverters); 62 [28.3%] of the seroconverters were virally suppressed (viral load  $\leq 400$  copies/mL). Samples were tested using two laboratory-based assays (LAg-Avidity, BioRad-Avidity) and a point-of-care assay (Assanté HIV-1 Rapid Recency assay). A qualitative multi-drug assay was used to identify seroconverters on ART.

**Results:** Antiretroviral (ARV) drugs were detected in 49 (79%) of the 62 virally suppressed seroconverters indicating that they were on ART. Those suppressed on ART were more likely to have higher BioRad-Avidity values than viremic seroconverters ( $p=0.021$ ), consistent with the expected longer duration of HIV infection in those who were suppressed on ART by their first HIV-positive visit. In contrast, seroconverters who were suppressed on ART were more likely to have LAg-Avidity values <1.5 and less likely to have the long-term infected band on the rapid LAg assay than those who were viremic ( $p=0.0096$ ,  $p=0.00047$ , respectively). Seroconverters suppressed on ART were also more likely to have LAg-Avidity values <1.5 than those who were virally suppressed in the absence of ARV drugs ( $p=0.014$ ).

**Conclusion:** Early ART was not associated with lower BioRad-Avidity values. In contrast, individuals who started ART and were suppressed within the first year of infection were more likely to have lower reactivity as measured by the LAg-Avidity and Rapid LAg assays than those who were viremic. This may reflect down-regulation of HIV antibodies in those on ART. Lower LAg-Avidity values were also obtained more frequently when viral suppression was due to ARV drug use. This may reflect differences in antibody expression in those with natural vs. ART-induced viral suppression.

## 683 MISSED HIV & HCV SCREENING IN EMERGENCY-DEPARTMENT PATIENTS WITH OPIOID-USE DISORDER

Michael S. Lyons<sup>1</sup>, Marek C. Chawarski<sup>2</sup>, Richard Rothman<sup>3</sup>, Lauren Whiteside<sup>4</sup>, Ethan Cowan<sup>5</sup>, Lynne D. Richardson<sup>6</sup>, Kathryn Hawk<sup>2</sup>, Judith I. Tsui<sup>7</sup>, Robert P. Schwartz<sup>8</sup>, Patrick O'Connor<sup>9</sup>, Gail D'Onofrio<sup>9</sup>, David A. Fiellin<sup>9</sup>, Jennifer E. Edelman<sup>9</sup>

<sup>1</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>2</sup>Yale University, New Haven, CT, USA, <sup>3</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>4</sup>University of Washington, Seattle, WA, USA, <sup>5</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA, <sup>6</sup>IBM Research—Zurich, Zurich, Switzerland, <sup>7</sup>University of Washington School of Medicine, Seattle, WA, USA, <sup>8</sup>Friends Research Institute, Baltimore, MD, USA, <sup>9</sup>Yale School of Medicine, New Haven, CT, USA

**Background:** Individuals with untreated opioid use disorder (OUD) are at substantial risk for HIV and hepatitis C virus (HCV). Emergency departments (EDs) provide a promising opportunity to screen high-risk populations and have made progress in screening program implementation. We evaluated HIV and HCV screening among ED patients with untreated OUD.

**Methods:** This cross-sectional analysis used data from a multi-site, hybrid type III effectiveness-implementation study to promote buprenorphine initiation in four large, urban, academic EDs. Structured screening programs, separate from but concurrent with the primary study, were in place for HIV at all sites and HCV at three sites. Consenting participants, enrolled between February 2017 and

January 2019, were adult, English-speaking ED patients who met Diagnostic and Statistical Manual (DSM)-5 criteria for OUD and were not receiving addiction treatment. Study assessments included self-reported sociodemographics, presence of medical provider for usual care, self-reported HIV and HCV status, and HIV/HCV related risk behaviors, as well as chart review to determine receipt of HIV or HCV screening during the ED encounter at which study enrollment occurred. Individuals reporting both HIV and HCV infection were excluded from analysis. Descriptive statistics were used to determine the proportion tested overall, by injection drug use (IDU) in the past month, and by ED site.

**Results:** Among 394 enrolled participants, 38% reported having a medical provider for usual care. There were 375 without reported HIV positive status, of whom 59 (16%) received an ED HIV test. Of 218 participants without known HIV who reported IDU, 33 (15%) were tested for HIV. There were 231 without reported HCV positive status, of whom 22 (9.5%) received an ED HCV test. Of 98 participants without known HCV who reported IDU, 9 (9%) were tested for HCV. The proportion tested across study sites ranged from 3% to 25% for HIV and 4% to 32% for HCV.

**Conclusion:** ED HIV and HCV screening remains insufficient among patients with untreated OUD, including those who inject drugs, even in ED settings with formal screening programs. Targeted HIV/HCV screening in EDs should be implemented as an important adjunct strategy until the ideal of universal screening can be more fully achieved, particularly given low rates of routine medical care in this population.

684

#### SUSTAINED 97% HIV TESTING RATE IN THE EMERGENCY DEPARTMENT: THE NEW GOLD STANDARD

Linda Cheyenne Vaccari<sup>1</sup>, Sarah Parry<sup>1</sup>, Deborah Kirkham<sup>1</sup>, Steven Pike<sup>1</sup>, Leslie Perry<sup>1</sup>, Andrew Widdowson<sup>1</sup>, Sarah Home<sup>1</sup>, Ian Cormack<sup>1</sup>

<sup>1</sup>Croydon University Hospital, London, UK

**Background:** UK 2020 HIV guidelines recommend opt-out HIV testing in Emergency Departments (ED) in areas of high prevalence (>2/1000). Our area has a very high HIV prevalence (>5/1000) with a 46% late diagnosis rate. We implemented opt-out testing in our ED in May 2020, sustaining testing rates of 97%.

**Methods:** All patients aged ≥16 undergoing venesection in ED have an HIV test automatically added. A separate blood sample is tested using Roche 4th generation HIV 1/2 antigen-antibody combination test. Posters and leaflets are prominently displayed in ED, signposting how to opt-out. IT blocks duplicate testing and those opted-out within the past 6 months. The HIV team receives an automated daily report of all non-negative HIV results. Patients not engaged in care are contacted. Those with new reactive tests are invited to attend for full sexual health screening including point of care test (POCT); if positive, patients are counselled pending confirmatory results and linked to HIV care that day with baseline bloods taken.

**Results:** 24,621/25,336 (97%) eligible patients were tested. This data excludes 21 days when Covid-19 reagent shortages halted testing. 244 patients had non-negative results. 161 were already engaged in care. 14 had defaulted care; nine have now re-engaged. 15 patients were confirmed new HIV diagnoses; 13 are now engaged in care and receiving antiretrovirals and two have declined care. 8/14 (57%) new patients and 5/9 (56%) defaulters had a CD4 count <200. 9/13 (69%) new patients had missed diagnostic opportunities. 42/244 (17%) patients with reactive tests were verified as false positives. 12 patients are awaiting repeat testing. Seven regular partners of newly diagnosed patients were verified HIV negative and managed with post- or pre-exposure prophylaxis, condoms and/or treatment as prevention. In the same period, ED diagnosed 15 patients compared to 12 non-ED (eight sexual health, one antenatal, two haematology, one medical). Our tested ED HIV prevalence is 7.72/1000 compared to a local recorded prevalence of 5.84/1000 ( $p < 0.0002$ ).

**Conclusion:** Collaborative working between ED, pathology, IT and HIV can sustain 97% testing rates using opt-out testing. The prevalence of HIV in ED attendees is statistically significantly higher than the local prevalence underlining the importance of HIV testing in ED. Wider benefits include earlier HIV diagnosis, reduced morbidity, mortality, investigations and healthcare costs, reduced length of stay, and reduced onward transmission.

| Gender | Age | Birth Country | Reason for ED attendance  | CD4 (%)    | HIV Viral Load |
|--------|-----|---------------|---------------------------|------------|----------------|
| M      | 28  | Ghana         | Gastroenterology          | 732 (36%)  | <50            |
| M      | 34  | UK            | Psychiatric               | 527 (28%)  | 255,000        |
| M      | 52  | Portugal      | Gastroenterology          | 181 (18%)  | 413,000        |
| M      | 28  | UK            | Trauma                    | 1180 (35%) | 368            |
| F      | 35  | Cameroon      | Neurology                 | 154 (11%)  | 11,200         |
| M      | 35  | Albania       | Respiratory               | 492 (32%)  | 4,450          |
| M      | 64  | Nigeria       | Neurology                 | 54 (4%)    | 211,000        |
| M      | 43  | Portugal      | Ophthalmology/Dermatology | 99 (13%)   | 1,350,000      |
| F      | 22  | Ghana         | Gynaecology               | 742 (34%)  | 1,930          |
| M      | 31  | Brazil        | Neurology                 | Unknown    | Unknown        |
| M      | 48  | Brazil        | Infection                 | 115 (12%)  | 350,000        |
| M      | 53  | Germany       | Infection/Dermatology     | 84 (7%)    | 185,000        |
| F      | 54  | Ghana         | Multisystem               | 167 (12%)  | 337,000        |
| M      | 51  | Unknown       | Respiratory               | Unknown    | <50            |
| F      | 36  | Cameroon      | Gynaecology               | 188 (15%)  | 23,200         |

Table 1: Demographics and baseline information for newly diagnosed patients

#### 685 HIV/STI TESTING AND PrEP ELIGIBILITY AMONG WOMEN INCARCERATED IN AN URBAN COUNTY JAIL

Jui Desai<sup>1</sup>, Ank Nijhawan<sup>2</sup>, Douglas Krakower<sup>3</sup>, Barry-Lewis Harris<sup>1</sup>, Dena Taherzadeh<sup>1</sup>

<sup>1</sup>Parkland Health and Hospital Systems, Dallas, TX, USA, <sup>2</sup>University of Texas Southwestern, Dallas, TX, USA, <sup>3</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA

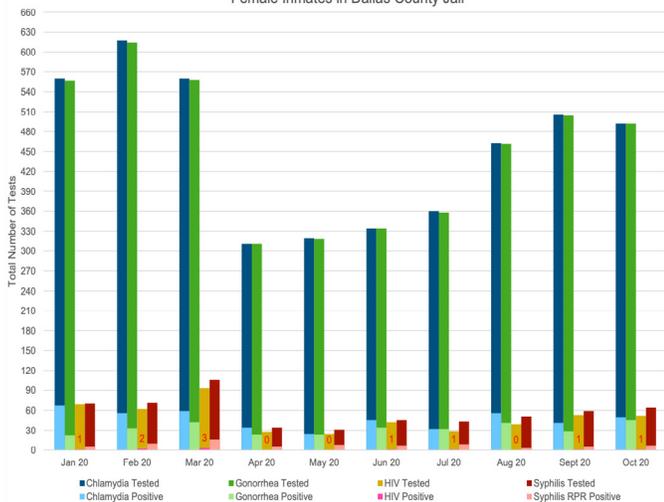
**Background:** Women in the criminal justice (CJ) system experience higher rates of HIV infection compared to both men in the CJ system and non-CJ involved women, due to high-risk factors and are eligible for pre-exposure prophylaxis (PrEP), though limited data exist on the implementation of PrEP in this population.

**Methods:** The results of all Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (GC) urine and HIV/Syphilis testing in women in the Dallas County Jail (DCJ) were compiled from January to October 2020. Electronic medical records (EMR) from the DCJ for a month-long period (March 2020) were manually reviewed and data collected regarding age, substance use, homelessness, patient request for STI testing, and time between GC/CT and HIV/syphilis results.

**Results:** From January to October 2020, 4398 females were tested for CT and 4389 for GC, and among this group, 479 (11%) were also tested for HIV and 562 (13%) for syphilis. Of women tested, median age was 42, and 462/4398 (11%) were positive for CT, 323/4389 (7%) positive for GC, 10/479 (2%) women had positive HIV tests, of whom 6 (1.3%) were new diagnoses and 75 (13%) had a reactive rapid plasma regain test. In March, 541 women were tested for CT and GC, 90 of whom tested positive for either CT or GC. Of these 90, the vast majority, 70 (78%) did not receive testing for HIV or syphilis, including women with the following risk factors: 4 (6%) were pregnant, 10 (14%) were homeless, 19 (27%) had requested STI/HIV testing at jail intake, 11 (16%) reported heroin use and 10 (14%) reported methamphetamine use. Individuals tested for all four infections (CT/GC/HIV/syphilis) were incarcerated for a longer period of time compared to those not tested for HIV/syphilis (83 v 30 days), with median time to HIV/syphilis testing after GC/CT result at 11 days.

**Conclusion:** Women incarcerated at a county jail had high rates of STIs and multiple other HIV risk factors, though only 1 in 5 with acute STIs (11% overall) were tested for HIV or syphilis. Efforts to improve HIV prevention in this high-risk, vulnerable population should include expansion of HIV testing, through paired STI and HIV testing offered early during incarceration, and utilization of automated EMR tools to highlight women who are PrEP candidates, like those testing positive for bacterial STIs or those with active substance use. Identification of those with elevated HIV risk, followed by counseling and linkage to PrEP care, could have a major impact on HIV prevention for incarcerated women.

Implementation and Results of STI Testing From January 2020–October 2020 in Female Inmates in Dallas County Jail



**686 ARE WE REACHING THE AT-RISK PATIENT POPULATIONS FOR HIV AND OTHER STIs?**

**Christoph Boesecke**<sup>1</sup>, Torben Kimhofer<sup>2</sup>, Christopher Tocha<sup>3</sup>, Oliver Schubert<sup>3</sup>, Rainer Rybak<sup>3</sup>, Klaus Kuhlen<sup>1</sup>, Christoph Klaes<sup>3</sup>, Jürgen K. Rockstroh<sup>1</sup>  
<sup>1</sup>Bonn University Hospital, Bonn, Germany, <sup>2</sup>Murdoch University, Murdoch, Australia, <sup>3</sup>AIDS-Hilfe Cologne, Cologne, Germany

**Background:** Published clinical and epidemiological data on individuals persons 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.

**Methods:** From January 2017 to December 2019, 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 11,456 visitors aged 16 to 85 years. Three main reasons were identified: recent HIV risk situation (46%), routine testing (29%), beginning of a new relationship (24%). The largest visitor group constituted men who have sex with men (MSM, 44%), followed by men who have sex with women (MSW, 29%), women having sex with men (WSM, 22%). MSM engaged on average with a higher number of sex-partners than MSW and WSM with 36% having 2-5 sex-partners and 10% having ≥ 26 per year. The annual number of visitors on PrEP (96% MSM) increased steadily, with a total of 29 visitors in 2017, 54 in 2018 and 123 in 2019 (p<0.001). The MSM group had the highest disease frequency (chlamydia: 140, gonorrhea: 123, syphilis: 88, HIV: 56, HCV: 2). STI frequency in PrEP users was highest for chlamydia/gonorrhoea (7%, 9% and 12% for 2017, 2018 and 2019, respectively). One PrEP user tested positive for HIV. In all other groups, chlamydia was the most prevalent infection while both HCV cases occurred among MSM. Despite increased PrEP prevalence in Germany since 2017 (covered by health insurance from 09/2019 onwards) no decline in HIV infection rates was observed with 20, 29 and 24 cases in 2017, 2018 and 2019, respectively (p=0.46). 56 new HIV infections were seen in MSM, 4 in MSW, 7 in WSM. 58% of newly diagnosed individuals indicated that a significant risk situation had occurred in the recent past, followed by 33% indicating routine testing.

**Conclusion:** Checkpoint was able to detect relevant STIs in 5% of all visitors thereby underling the importance of community-based testing sites. Despite increased HIV awareness and PrEP roll-out MSM remain at highest risk for contracting HIV (and HCV) highlighting the continuous need for educational activities as well as low-threshold and cost-free STI screening capacities.

**687 DECREASED HIV TESTING BEFORE HIV DIAGNOSIS AMONG BLACKS/ AFRICAN AMERICANS: US 2013-18**

**Sonia Singh**<sup>1</sup>, Xueyuan Dong<sup>2</sup>, Laurie Linley<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>ICF International, Atlanta, GA, USA

**Background:** In 2018, Blacks/African Americans (Blacks) accounted for 13% of the US population and 42% of new HIV diagnoses. Ensuring high levels of HIV testing is essential in reducing disparities in HIV diagnoses and decreasing the rate of HIV infection in Blacks. Our analysis elucidates which subgroups may benefit from increased testing, leading to linkage to care and improvement in HIV care outcomes.

**Methods:** We used NHSS data to assess trends in HIV testing patterns among Blacks aged ≥13 years with HIV infection diagnosed from 2013–2018 by sex, age and transmission category. HIV testing history data were collected by 21 sites participating in HIV incidence surveillance. The estimated annual percent change (EAPC) and 95% CIs were used to assess trends from 2013–2018.

**Results:** The number of Blacks with diagnosed HIV infection was 11,742 in 2013 and 10,881 in 2018 and the percentage with any testing history was 66% in 2013 and 61% in 2018. Among Blacks with testing history, the percentage who ever had a previous negative HIV test decreased significantly from 66% in 2013 to 58% in 2018 [EAPC=-2.5,95%CI(-3.2,-1.8)]. Significant decreases occurred for males and females. By age, significant decreases occurred for those aged 13-24, 25-34 and 35-44 years. Among Blacks with infection attributed to male to male sexual contact, the percentage who had a previous negative HIV test decreased significantly from 70% to 62% [EAPC=-2.3,95%CI(-3.1,-1.4)]. Among those with infection attributed to heterosexual contact, the percentage who had a previous negative HIV test decreased significantly from 54% to 44% [EAPC=-3.8,95%CI(-6.1,-1.4)] for males and from 62% to 52% [EAPC=-3.7,95%CI(-5.2,-2.2)] for females. Among Blacks with a known negative HIV test date before HIV diagnosis, the trend in the percentage of those with a negative test ≤12 months before diagnosis remained stable overall (mean 49% per year) and was also stable for all sex, age and transmission categories.

**Conclusion:** There is decreased HIV testing among Blacks overall, for males and females and those with infection attributed to male to male sexual contact and heterosexual contact. The percentage with a negative test ≤12 months before diagnosis remained stable for all groups. Annual HIV testing should be promoted among Blacks at higher risk of infection to increase early detection of HIV infection, and also to increase linkage as a means for improving HIV care outcomes and reducing risk for HIV transmission.

**688 TIMELY HIV CASE AND SEQUENCE REPORTING FOR CLUSTER DETECTION: UNITED STATES**

**Kathryn Curran**<sup>1</sup>, Neeraja Saduvala<sup>1</sup>, Laurie Linley<sup>1</sup>, Anne H. Peruski<sup>1</sup>, Anne Marie France<sup>1</sup>, Alexandra M. Oster<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** Responding quickly to potential HIV outbreaks, a pillar of the U.S. Ending the HIV Epidemic (EHE) initiative, requires timely HIV case and sequence reporting. Expediting reporting of case reports, needed to detect clusters of increased diagnoses, and HIV sequence data, needed to detect molecular clusters, will be a key activity in EHE-funded programs. We describe the baseline timeliness of HIV case and sequence reporting to health departments overall and by geographic characteristics.

**Methods:** Using data reported to the U.S. National HIV Surveillance System by December 2019 for persons ≥13 years with HIV diagnosed during 2018, we described the time from HIV diagnosis to entry into the local surveillance system of key information. Timely reporting was defined as entry of cases ≤30 days after diagnosis, and entry of sequence reports within 45 days of diagnosis.

**Results:** Among 37,428 HIV diagnoses in 2018, 21,982 (59%) were entered ≤30 days after diagnosis. Median time to entry was 24 days (interquartile range [IQR]: 5.5–42.5) and varied by jurisdiction (range: 5–134). A higher proportion of HIV diagnoses met timely case reporting standards in: nonmetropolitan (71%) and small metropolitan areas (70%); the Midwest (69%) and South (66%); and jurisdictions not included in phase 1 EHE funding (65%) (Table). Of 19,289 HIV diagnoses with sequences reported, 71% had a sample collected within 30 days of diagnosis. However, only 6% had sequence data entered into the surveillance system within 45 days (median: 74 days; IQR: 31.5–117.5), with wide variation by jurisdiction (9.5–470). Time from diagnosis to specimen collection (median: 15 days; IQR: 0–30) was shorter than time from specimen collection to receipt and entry by the health department (median: 48 days; IQR: 27–70).

**Conclusion:** Over half of HIV diagnoses in 2018 were reported to the health department within one month, allowing analyses to detect clusters of increased diagnoses for further investigation. Reporting delays were greater for large metropolitan areas, the West, and the Northeast. Delayed availability of sequence results, which has implications for detecting molecular clusters, is driven by reporting rather than physician ordering of drug resistance testing, suggesting potential for improvement with changes in laboratory reporting and informatics practices. Additional EHE funding can be used to improve processes to expedite reporting and entry of case, laboratory, and key data into surveillance systems for real-time decision-making.

Table. Timely HIV case and sequence reporting of HIV diagnoses in persons  $\geq 13$  years in the United States in 2018

|                                   |  | Timely HIV case report, entered $\leq 30$ days |             | No. HIV diagnoses with sequences, entered $\leq 45$ days |            |
|-----------------------------------|--|--|-------------|--|------------|
|                                   |  | No. HIV diagnoses (N=37428)                    | % (N=21982) | No. HIV diagnoses (N=19289)                              | % (N=1114) |
| Location of facility of diagnosis | Nonmetro areas (<50,000)                   | 1487   | 71          | 638  | 8          |
|                                   | Metro areas (50,000-499,999)               | 5649   | 70          | 2920   | 8          |
|                                   | Metro statistical areas ( $\geq 500,000$ ) | 30165  | 56          | 15696  | 5          |
|                                   | Unknown                                    | 127  | 28          | 35   | 3          |
| Region of Residence               | Northeast                                  | 5573   | 46          | 2931   | 7          |
|                                   | Midwest                                    | 4921   | 69          | 2500   | 8          |
|                                   | South                                      | 19422  | 66          | 9797   | 6          |
|                                   | West                                       | 7512   | 43          | 4061   | 4          |
| EHE jurisdiction*                 | Yes  | 21908  | 54          | 10975  | 5          |
|                                   | No   | 15520  | 65          | 8314   | 7          |

\*EHE: Ending the HIV Epidemic; a list of phase 1 jurisdictions can be accessed here: <https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/jurisdictions/phase-one>.

## 689 THE PLASMA SEPARATION CARD (PSC): A SUITABLE ALTERNATIVE TO PLASMA HIV-1 VIRAL LOAD

**Katrina Sleeman**<sup>1</sup>, Lucia Hans<sup>2</sup>, Guoqing Zhang<sup>1</sup>, Stephen Jadcak<sup>1</sup>, Lynette Makuwaza<sup>3</sup>, Keneilwe Peloakgosi-Shikwambani<sup>3</sup>, Mackenzie Hurlston Cox<sup>1</sup>, Heather Alexander<sup>1</sup>, Sergio Carmona<sup>2</sup>, Clement Zeh<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>National Health Laboratory Service, Johannesburg, South Africa, <sup>3</sup>Wits Health Consortium, Johannesburg, South Africa

**Background:** Cold chain and centrifugation requirements of plasma have limited the access of remote and vulnerable populations to HIV viral load (VL) testing. Roche Molecular Diagnostics developed a sample collection device, the plasma separation card (PSC) where plasma is obtained from the addition of whole blood to the PSC, eliminating the need for centrifugation and cold chain. We sought to independently evaluate the analytical and clinical performance of the PSC as an alternative matrix for HIV-1 VL across multiple Roche testing platforms for WHO prequalification and for use in President's Emergency Plan for AIDS Relief (PEPFAR) countries.

**Methods:** Performance of PSC dried plasma spots were compared to centrifuged plasma samples using HIV negative whole blood spiked with cultured virus or using the third HIV-1 International WHO Standard and remnant clinical samples submitted for HIV VL testing. Prepared dried plasma spots were tested within 56 days using the COBAS® AmpliPrep/COBAS® TaqMan® (CAP/CTM) HIV-1 Test, v2, and the cobas® HIV-1 test on the cobas® 4800 (c4800) and 6800/8800 (c6800/8800) platforms. The limit of detection (LOD) was calculated using PROBIT analysis. The precision of measurement, cross-contamination, and linearity for subtypes A, B, C, D and CRF02-AG were also determined. Bland-Altman and correlation analysis were applied to evaluate clinical performance of the PSC on the c4800 and the c6800/8800.

**Results:** The LOD for PSC samples was calculated to be 579.3, 745.2, and 489.4 copies/mL on the CAP/CTM, c4800 and c6800/8800 respectively. No cross-contamination was detected on any platform among the 40 samples tested, alternating between 20 high positive and 20 negative samples. Standard deviation between runs for all three platforms was within 0.14 log<sub>10</sub> copies/mL. Linearity assessment of HIV-1 subtypes A, B, C, D and CRF02-AG showed R2 values greater than 0.98 for all three platforms. Invalid rates using the PSC were below 5%. When compared to centrifuged plasma, the PSC had a demonstrated sensitivity of 96% and 95% and a specificity of 94% and 97% on the c4800 and c6800/8800, respectively. The average bias between PSC and plasma was less than 0.2 log<sub>10</sub> copies/mL for the c4800 and c6800/8800.

**Conclusion:** These findings reveal the PSC as a suitable alternative to plasma HIV-1 VL for monitoring patients on antiretroviral treatments in remote settings and in low- and middle-income countries. This PSC evaluation contributed to WHO prequalification and PEPFAR approval.

## 690 CORONACHEK SARS-CoV-2 POINT-OF-CARE ANTIBODY TEST PERFORMANCE IN UGANDA AND BALTIMORE

**Owen R. Baker**<sup>1</sup>, M. Kate Grabowski<sup>2</sup>, Ronald Galiwango<sup>3</sup>, Aminah Nalumansi<sup>4</sup>, Jennifer Serwanga<sup>4</sup>, William Clarke<sup>2</sup>, Yu-Hsieh Hsieh<sup>2</sup>, Richard Rothman<sup>2</sup>, David Serwadda<sup>5</sup>, Joseph Kagaayi<sup>3</sup>, Tom Lutalo<sup>3</sup>, Steven J. Reynolds<sup>1</sup>, Pontiano Kaleebu<sup>4</sup>, Thomas Quinn<sup>1</sup>, Oliver Laeyendecker<sup>1</sup>

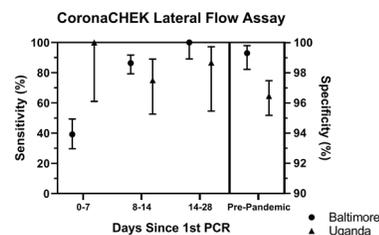
<sup>1</sup>National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Rakai Health Sciences Program, Kalisizo, Uganda, <sup>4</sup>Uganda Virus Research Institute, Entebbe, Uganda, <sup>5</sup>Makerere University School of Public Health, Kampala, Uganda

**Background:** The performance of serological antibody tests to SARS-CoV-2 infection varies widely and little is known about their performance in Africa. We assessed the performance of CoronaCHEK Lateral Flow Point of Care Tests on samples from Rakai, Uganda and Baltimore, Maryland, USA.

**Methods:** Samples from subjects known to be SARS-CoV-2 PCR+ (Uganda: 50 samples from 50 individuals, and Baltimore: 266 samples from 38 individuals) and samples from pre-pandemic individuals collected prior to 2019 (Uganda: 1077 samples, Baltimore: 580 samples) were analyzed with the CoronaCHEK assay per manufacturers protocol. Sensitivity by duration of infection and specificity among pre-pandemic samples were assessed for the IgM and IgG bands separately and for any reactivity. Poisson regression models were used to calculate prevalence ratios (PR) for factors associated with a false-positive test among pre-pandemic samples.

**Results:** In Baltimore samples, sensitivity for any reactivity increased with duration of infection with 39% (95% CI 30, 49) during 0-7 days since first positive PCR, 86% (95% CI 79, 92) for 8-14 days, and 100% (95% CI 89,100) after 15 days (See Figure). In Uganda, sensitivity was 100% (95% CI 61,100) during 0-7 days, 75% (95% CI 53, 89) for 8-14 days, and 87% (95% CI 55, 97) after 14 days since first positive PCR. Specificity results among pre-pandemic samples from Uganda was 96.5% (95% CI 97.5, 95.2), significantly lower than the 99.3% (95% CI 98.2, 99.8) observed in samples from Baltimore (p<0.01). In Ugandan samples, individuals with a false positive result were more likely to have had a fever more than a month prior to sample acquisition (PR 2.9, 95% CI 1.1, 7.0).

**Conclusion:** Sensitivity of the CoronaCHEK appeared to be significantly higher in Ugandan samples from individuals within their first week of infection compared to their Baltimore counterparts. By the second week of infection the sensitivity appeared the same between geographic areas. The specificity was significantly lower in Ugandan samples than those from Baltimore. False positive results from pre-pandemic Uganda appear to be correlated with the convalescent disease state, potentially indicative of a highly cross-reactive immune response in these individuals from East Africa.



## 691 COST-EFFECTIVENESS OF SARS-CoV-2 RAPID ANTIGEN TESTING IN LOW-RESOURCE SETTINGS

**Sarah J. Girdwood**<sup>1</sup>, Sergio Carmona<sup>2</sup>, Emma Hannay<sup>2</sup>, Brooke Nichols<sup>3</sup>  
<sup>1</sup>Health Economics and Epidemiology Research Office, Johannesburg, South Africa, <sup>2</sup>Foundation for Innovative New Diagnostics, Geneva, Switzerland, <sup>3</sup>Boston University, Boston, MA, USA

**Background:** The World Health Organization (WHO) has called for increased testing to help arrest the transmission of coronavirus disease 19 (COVID-19). Molecular testing (PCR) is the recommended method for the diagnosis of COVID-19. In low-resource settings (LRS) however, the availability and public health impact of these tests is constrained by availability of testing capacity, shortages of reagents/supplies, lack of skilled personnel, long turnaround times (TAT), and costs. Despite lower sensitivity, antigen detection rapid diagnostic tests (AgRDTs) could provide improved access at lower costs and quicker TAT. We evaluated the optimal use of AgRDTs to increase testing access within TAT and reduce the cost and the number of cases missed in LRS.

**Methods:** We modeled estimated COVID-19 testing demand coverage based on current PCR capacity in three different epidemic phases across five African countries (Strategy 1). We then modelled five additional testing strategies that utilized a combination of PCR and AgRDT: 2)replacing current PCR coverage with AgRDT; 3)saturating testing demand with AgRDT only; 4)saturating testing demand first with PCR then the remainder with AgRDT; 5)saturating testing demand with AgRDT and reflex testing with PCR for patients at risk of severe disease; 6)constrained by budget of Scenario 1, using a mix of PCR and AgRDT. We estimated the total number of correct test results expected within a 48hr TAT, corresponding costs (assuming \$12/PCR and \$6/AgRDT), and the incremental cost-effectiveness ratios for each strategy and epidemic phase by country.

**Results:** Across all countries and phase of epidemic, there was insufficient PCR capacity to meet the calculated required testing demand within a 48hr TAT (ranging from 0-20%) (Figure). In no instance was the base case strategy that was limited to current PCR capacity considered cost-effective (CE). Strategy 3, in which testing demand was saturated with AgRDT, was considered robustly CE in every epidemic phase (\$4-\$7 per additional person with a correct test result within 48hr TAT), and would require both a large increase in budget and wide AgRDT availability. Additional strategies on the CE frontier were country and epidemic-phase specific.

**Conclusion:** Inclusion of AgRDT in testing strategies is CE and critical in increasing timely testing access in countries with low PCR capacity. Given the importance of timely results for epidemic control, future work should quantify the epidemic impact of saturating testing demand in LRS.

**Figure.** Cost and coverage of testing requirement with a correct test result within a 48-hour turnaround time of six PCR and AgRDT testing strategies in five African countries across three different phases of the SARS-CoV-2 pandemic

| Country                          | Strategy | Low to Peak or Peak to low pandemic month |                     |                     | Low to Peak or Peak to low pandemic month |                     |                     |
|----------------------------------|----------|---|---------------------|---------------------|---|---------------------|---------------------|
|                                  |          | Low epidemic month                        | Peak pandemic month | Peak pandemic month | Low epidemic month                        | Peak pandemic month | Peak pandemic month |
| Central African Republic         | 1        | 0%  | 0%                  | 0%                  | 9%  | 3%                  | 2%                  |
|                                  | 2        | -50%                                      | -50%                | -50%                | 29%                                       | 11%                 | 5%                  |
|                                  | 3        | 67%                                       | 337%                | 783%                | 98%                                       | 96%                 | 91%                 |
|                                  | 4        | 117%                                      | 387%                | 833%                | 77%                                       | 89%                 | 87%                 |
|                                  | 5        | 145%                                      | 421%                | 877%                | 94%                                       | 96%                 | 91%                 |
|                                  | 6        | 0%  | 0%                  | 0%                  | 50%                                       | 19%                 | 9%                  |
| Democratic Republic of the Congo | 1        | 0%  | 0%                  | 0%                  | 1%  | 0%                  | 0%                  |
|                                  | 2        | -50%                                      | -50%                | -50%                | 3%  | 1%                  | 0%                  |
|                                  | 3        | 1810%                                     | 5138%               | 10520%              | 98%                                       | 96%                 | 91%                 |
|                                  | 4        | 1860%                                     | 5188%               | 10570%              | 96%                                       | 96%                 | 90%                 |
|                                  | 5        | 1910%                                     | 5238%               | 10620%              | 98%                                       | 96%                 | 91%                 |
|                                  | 6        | 0%  | 0%                  | 0%                  | 4%  | 2%                  | 1%                  |
| Ethiopia                         | 1        | 0%  | 0%                  | 0%                  | 10%                                       | 3%                  | 1%                  |
|                                  | 2        | -50%                                      | -50%                | -50%                | 32%                                       | 10%                 | 5%                  |
|                                  | 3        | 52%                                       | 379%                | 906%                | 98%                                       | 96%                 | 91%                 |
|                                  | 4        | 102%                                      | 429%                | 956%                | 75%                                       | 89%                 | 87%                 |
|                                  | 5        | 120%                                      | 457%                | 1001%               | 87%                                       | 95%                 | 91%                 |
|                                  | 6        | 0%  | 0%                  | 0%                  | 55%                                       | 17%                 | 8%                  |
| Nigeria                          | 1        | 0%  | 0%                  | 0%                  | 2%  | 1%                  | 0%                  |
|                                  | 2        | -50%                                      | -50%                | -50%                | 7%  | 2%                  | 1%                  |
|                                  | 3        | 643%                                      | 2123%               | 4475%               | 98%                                       | 96%                 | 91%                 |
|                                  | 4        | 693%                                      | 2173%               | 4525%               | 93%                                       | 95%                 | 90%                 |
|                                  | 5        | 743%                                      | 2223%               | 4575%               | 98%                                       | 96%                 | 91%                 |
|                                  | 6        | 0%  | 0%                  | 0%                  | 11%                                       | 4%                  | 2%                  |
| South Africa                     | 1        | 0%  | 0%                  | 0%                  | 20%                                       | 11%                 | 6%                  |
|                                  | 2        | -50%                                      | -50%                | -50%                | 65%                                       | 36%                 | 20%                 |
|                                  | 3        | -25%                                      | 34%                 | 141%                | 98%                                       | 96%                 | 90%                 |
|                                  | 4        | 25%                                       | 84%                 | 191%                | 53%                                       | 71%                 | 77%                 |
|                                  | 5        | 43%                                       | 106%                | 216%                | 76%                                       | 87%                 | 87%                 |
|                                  | 6        | -10%                                      | 0%                  | 0%                  | 98%                                       | 61%                 | 34%                 |

Scenarios on the cost-effectiveness frontier

**692 CAN'T WORK FROM HOME: POOLED NUCLEIC ACID TESTING OF LABORATORY WORKERS DURING COVID**

**Stephen A. Rawlings<sup>1</sup>, Brianna Scott<sup>1</sup>, Laura Layman<sup>1</sup>, Pramod Naranatt<sup>2</sup>, Roy Hetsley<sup>3</sup>, Caroline Ignacio<sup>1</sup>, Magali Porrachia<sup>1</sup>, Sara Gianella<sup>1</sup>, Antoine Chaillon<sup>1</sup>, Davey M. Smith<sup>1</sup>**

<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>Flanders Institute of Biotechnology, Flanders, Belgium, <sup>3</sup>Fluxergy, Irvine, CA, USA

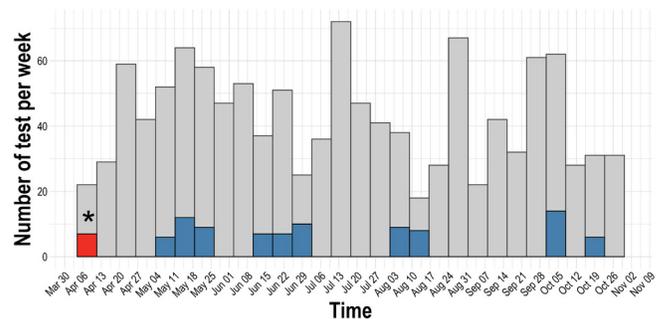
**Background:** Closing labs to decrease spread of COVID-19 has impacted research progress. Serial testing could supplement other measures to help provide a safe lab environment.

**Methods:** Lab employees who came to work at an academic laboratory at the University of California San Diego (UCSD) were invited and consented to

perform their own anterior nasal swab or have a swab collected by an on-site physician. Nasal swabs were combined into one pool for each work shift. Each pool underwent nucleic acid testing (NAT) via qRT-PCR to detect SARS-CoV-2 RNA (FluxErgy). Results were available within one hour. Positive pools were deconvoluted and tested individually. Cost evaluation of the pooling approach was compared to individual NAT and to institutional guidelines for lab occupancy.

**Results:** From Apr 9 to Oct 26, 2020 (28 weeks), 1,199 nasal swab samples collected from lab workers were batched in 194 pools of median size 7 [95%: 3-11]. A median of 41 tests per week [95%: 22-67] were performed in a total of 77 participants (Fig 1). 19 core staff were tested a median 54 times [95%:13-95]. Of the 194 pools, 7 (3.6%, n=47 samples) were considered positive and required repeat testing of all participant samples in the pool as confirmation. One true positive was identified before work started. That participant was referred to their primary care provider. This early detection prevented a 2-week quarantine of 7 employees. Given ~\$65/hour salary per lab worker, this saved 420 hours of work and ~\$26,600 in wages. Current UCSD guidelines recommend decreasing staffing levels to 25% of pre-COVID-19 occupancy. Regular NAT allowed 100% staffing. Screening of lab technicians with the pooled NAT strategy over 6 months cost \$25,740 but permitted 2,430 person-hours of additional work (\$132,210 in wages), as compared to the recommended 75% reduction without testing. A similar approach with individual NAT would cost \$124,020 (thus \$98,280 saved by pooling).

**Conclusion:** Regular pooled NAT for SARS-CoV-2 among lab personnel offers a cost-efficient way to maintain a safe lab environment without a reduction in staffing. This approach could be applied in other settings to help ensure safe work environments.



**Figure 1.** Number of SARS-CoV-2 tests performed per week in the six months from April 9 to October 28, 2020 in an academic lab. Swabs were pooled from participants working in the lab. Grey bars are negative tests. Blue bars represent pools that were flagged as positive but later determined to be false positive tests. One pool (red bar, \*) was positive and deconvoluted to identify a single true positive.

**693 NEUTRALIZING ANTIBODY DECAY IN PATIENTS WITH MILD OR ASYMPTOMATIC COVID-19 INFECTION**

**Adele Boccutto<sup>1</sup>, Francesca Gatti<sup>2</sup>, Renzo Scaggiante<sup>2</sup>, Eliana Modolo<sup>2</sup>, Daniela Zago<sup>3</sup>, Monica Basso<sup>3</sup>, Filippo Dragoni<sup>1</sup>, Nicolò Bartolini<sup>1</sup>, Ilaria Vicenti<sup>1</sup>, Maurizio Zazzi<sup>1</sup>, Saverio G. Parisi<sup>3</sup>**

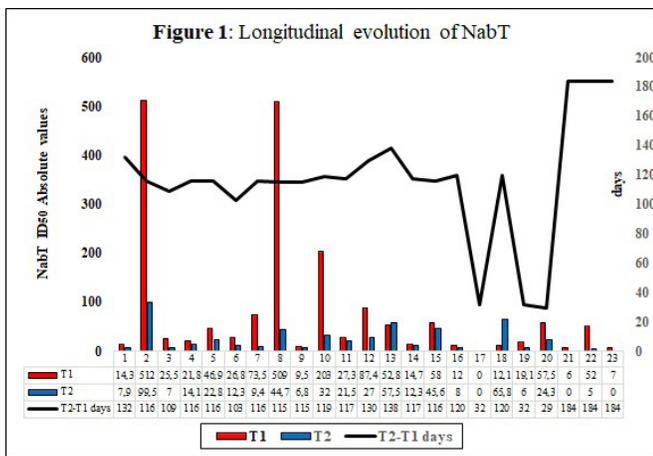
<sup>1</sup>University of Siena, Department of Medical Biotechnologies, Siena, Italy, <sup>2</sup>Belluno Hospital, Belluno, Italy, <sup>3</sup>University of Padova, Department of Molecular Medicine, Padova, Italy

**Background:** Development of neutralizing antibody (Nab) is crucial for protection from SARS-CoV-2 reinfection. The aim of the study was to analyze Nab titers (NabT) and kinetics over time in a cohort of 85 unselected not hospitalized Italian subjects (pts) with COVID-19 infection, with mild or no symptoms, tested after symptoms onset or for surveillance of healthcare workers.

**Methods:** Two-fold serial dilutions of heat-inactivated sera were incubated with 100 TCID50 of SARS-CoV-2 virus (lineage B) at 37°C for 1 h in 96-wells plates. Then, pre-seeded 10,000 Vero E6 cell lines per well (ATCC CRL-1586) were treated with serum-virus mixtures and incubated at 37°C. After 72h, cell viability was determined through the commercial kit Cell-titer Glo 2.0 (Promega). The NabT was defined as the reciprocal value of the sample dilution that showed a 50% protection of virus cytopathic effect (ID50). NabT ≥ 5 ID50 were defined as SARS-CoV-2 positive and neutralizing. Chi squared, Wilcoxon, Fisher's exact test and Spearman's correlation coefficient were used.

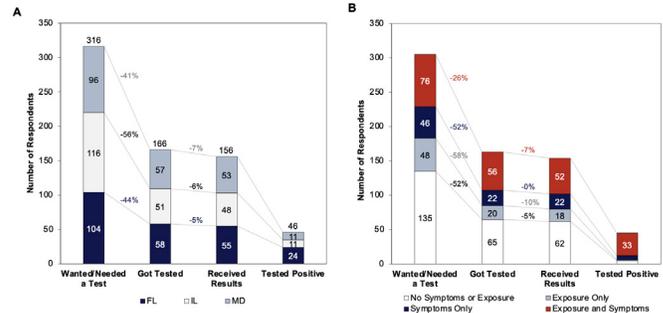
**Results:** Female were 57 (67.1%) and median age was 48 years. Pts were classified as early tested (ET, <60 days, n=40) and late tested (LT, >60 days, n=45). Overall, 30 (35.3%) pts had low (<10 ID50) NabT, 33 (38.8%) had intermediate NabT (ID50 11 to 50), and 22 (25.9%) had high NabT (ID50 >51, 9 of them >100). The frequency of each NabT class was comparable in ET and LT: low NabT was found in 11 (27.5%) and 19 (42.2%), intermediate in 16 (40%) and 18 (40%) and high in 13 (32.5%) and 8 pts (17.8%), respectively. However, no NabT higher than 200 ID50 was found in LT vs 5 in ET (p=0.04). No correlation between age and gender and NabT was found. At now, 23 pts had 2 NabT available during the follow up (T1 and T2); the interval between the two tests was 117 days (median). Almost all pts (20/23, 87%), showed NabT decrease: the median value of percentage decrease respect to the previous value was 63.2% (IQR 30.8-85.7) (p=0.0006). One pt had undetectable NabT at both times and two pts experienced an increase (Figure 1). No correlation between interval length, T2 value and percentage of decrease was observed.

**Conclusion:** One third of pts had a very low level of NabT regardless of test timing. After 60 days from diagnosis a subset of pts had a value >100 but no >200, differently from the first 60 days, suggesting that NabT level could be a useful tool for dating past infections. The observed decrease of NabT has implications for reinfection and vaccine.



primary reasons for testing were desire to know status (35%) and symptoms (28%). Among those tested, 53% had to wait ≥8 days to get a result from the time they wanted/needed a test. Of those tested, 71% reported quarantining while awaiting results. An additional 146 who wanted/needed a test did not get tested; the main reasons for not testing in this group were not knowing where to go (36%) and distance/waiting time (33%); an additional 21% reported fear of being tested.

**Conclusion:** These data reflecting similar testing barriers across three US states underscore the importance of a unified national strategy with clear messaging on who, where, when, and how to get a test, as well as improved turn-around-times. As demand rises borrowing strategies from HIV such as self-testing could help overcome logistical barriers.



**Figure.** SARS-CoV-2 testing cascade by (A) state and (B) self-reported symptoms. Trend lines and percentages reflect the proportion lost between each step in the cascade.

Note: Numbers may not sum to the total if there were participants who elected not to answer a given question.

**694 SARS-CoV-2 TESTING IN FLORIDA, ILLINOIS, AND MARYLAND: ACCESS AND BARRIERS**

**Steven J. Clipman<sup>1</sup>, Amy Wesolowski<sup>1</sup>, Shruti H. Mehta<sup>1</sup>, Smisha Agarwal<sup>1</sup>, Sarah E. Cobey<sup>2</sup>, Sunil S. Solomon<sup>3</sup>, Derek A. Cummings<sup>4</sup>**

<sup>1</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>University of Chicago, Chicago, Illinois, USA, <sup>3</sup>Johns Hopkins School of Medicine, Baltimore, MD, USA, <sup>4</sup>University of Florida, Gainesville, FL, USA

**Background:** Rapid detection and isolation of SARS-CoV-2 infections is critical to mitigate the pandemic; however, testing access across the US has been uneven and data on barriers to testing are limited.

**Methods:** We conducted serial cross-sectional assessments of experiences around SARS-CoV-2 PCR testing in Florida, Illinois, and Maryland. We sampled ~1000/state using an online survey from Jul 15–31 and Sep 16–Oct 15, 2020, with additional waves planned at 6–8 week intervals. At the time of surveys, there were no systematic differences in testing availability (public, private and free testing options) across these states. Participants were recruited using an online panel; demographic targets were provided to match age, sex, race/ethnicity and income distributions of each state. Participants were ≥18 years, provided consent, and resided in the study state. The survey covered demographics, symptoms, and PCR testing in the prior 2 weeks.

**Results:** Of 3,058 persons surveyed most recently (Sep 16–Oct 15), 316 (10%) reported wanting/needing a test in the prior two weeks. Median age of participants wanting/needing a test was 36 years and 46% were female; 47% self-identified as White and 57% reported working outside home. Of 316 who wanted/needed a test in the prior 2 weeks, 53% were able to get tested, of whom, 94% received results, with no significant differences by state (Figure); this was not substantially different from the proportion able to get tested in July (51%). Among those wanting/needing a test, getting tested was significantly less common among men (aOR: 0.46) and those reporting black race (aOR: 0.53) and more common in those reporting recent travel (aOR: 3.35; all p<0.05). The

**695 SIGNIFICANT IMPACT OF COVID-19 ON THE FIRST PILLARS OF THE HIV CARE CONTINUUM**

**Kathryn S. Hensley<sup>1</sup>, Carlijn Jordans<sup>1</sup>, Jan E. Van Beek<sup>1</sup>, Marion E. Vriesde<sup>1</sup>, Jeroen J. Van Kampen<sup>1</sup>, Charles A. Boucher<sup>1</sup>, Femke P. Mollema<sup>2</sup>, Elisabeth H. Gisolf<sup>3</sup>, Rachida El Moussaoui<sup>4</sup>, Gonke Hermandes<sup>5</sup>, Renee N. Finkenflugel<sup>6</sup>, Bart J. Rijnders<sup>1</sup>, Annelies Verbon<sup>1</sup>, Casper Rokx<sup>1</sup>**

<sup>1</sup>Erasmus University Medical Center, Rotterdam, Netherlands, <sup>2</sup>Haaglanden Medical Centre, The Hague, Netherlands, <sup>3</sup>Rijnstate Hospital, Arnhem, Netherlands, <sup>4</sup>Maastad Hospital, Rotterdam, Netherlands, <sup>5</sup>Red Cross Hospital, Beverwijk, Netherlands, <sup>6</sup>HIV Vereniging Nederland, Amsterdam, Netherlands

**Background:** After SARS-CoV-2 reached the Netherlands in February 2020, rapid interventions were taken to mitigate viral spread and optimise care for COVID-19 patients. Lockdowns and downscaling of regular healthcare practices were necessary to scale up COVID-19-related care. The effect of these interventions on HIV care are uncertain. We assessed the impact of the nationwide lockdown in March and May during the first COVID-19 wave on HIV diagnosis and linkage to care.

**Methods:** An observational study was conducted at the Erasmus MC, a regional reference tertiary hospital in the Netherlands. All patients ≥ 18 years presenting with HIV indicator conditions (ICs) were identified in electronic patient records, using an automated identification system for ICD-10 and health insurance codes. Primary outcomes measured were the number of HIV tests performed, number of HIV ICs and corresponding HIV testing rates, and new HIV diagnoses before, during and after lockdown.

**Results:** From January to April, all newly registered diagnoses decreased by 35%, and in patients referred for HIV ICs by 69% (figure 1). The proportion of patients presenting with HIV ICs that were adequately tested for HIV remained relatively stable, especially where HIV testing is standardised, even during lockdown in March, April and May when a cumulative 328 proven or suspected COVID-19 patients were admitted. The absolute number of HIV tests performed during the first half year of 2020 was 13% lower than the same period in 2019, and new HIV patient referrals dropped 67%. The number of HIV IC, HIV testing rates and HIV referrals showed recovery after the lockdown.

**Conclusion:** The first two pillars of the HIV care continuum were affected by the lockdown during the COVID-19 pandemic. Standardisation of HIV testing could prevent diagnostic delays to a certain extent. With an eye on subsequent COVID-19 waves, these data indicate that maintaining focus on adequate identification and testing of patients with undiagnosed HIV is essential to prevent unwanted declines affecting the 95-95-95 goals.

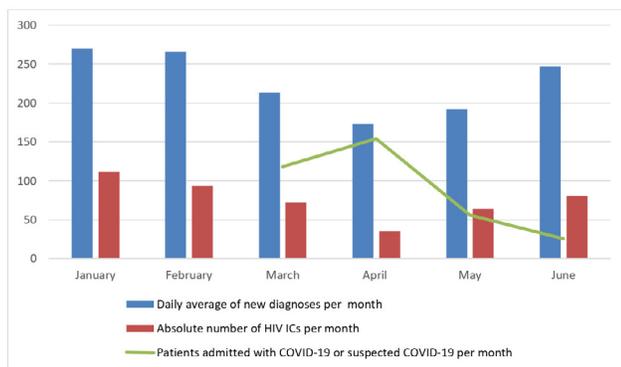


Figure 1: Average daily number of new diagnoses per month and absolute number of new HIV IC diagnoses per month in the first six months of 2020 with monthly absolute number of patients admitted with COVID-19 or suspected COVID-19.

**696 TRENDS IN TRUVADA AND DESCOVY PRESCRIPTIONS FOR PrEP IN THE UNITED STATES, 2014-2020**

**Karen W. Hoover**<sup>1</sup>, Weiming Zhu<sup>1</sup>, Jeffrey Wiener<sup>1</sup>, Ya-Lin A. Huang<sup>1</sup>  
<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

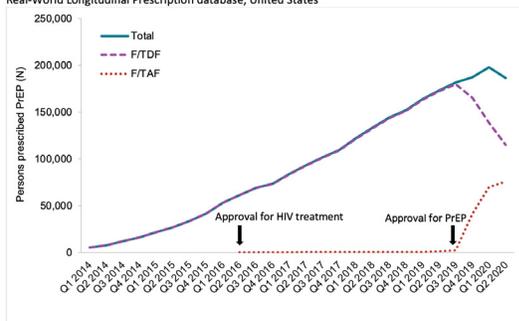
**Background:** Emtricitabine and tenofovir disoproxil fumarate (F/TDF) was the only PrEP drug available in the United States until the FDA approved emtricitabine and tenofovir alafenamide (F/TAF) for PrEP on October 3, 2019. Both drugs are safe and effective for PrEP. In 2018, the U.S. healthcare system spent \$2.1 billion on PrEP for 18% of persons with a PrEP indication. Less expensive generic formulations of F/TDF are expected in late 2021 when emtricitabine's patent expires. We estimated trends in the use of these drugs and switching from F/TDF to F/TAF.

**Methods:** We analyzed data from the IQVIA prescription database to estimate the number of persons prescribed F/TDF or F/TAF for PrEP by calendar quarter from January 2014 through June 2020. During October 1, 2019 through June 30, 2020, we estimated the proportion of new PrEP users prescribed F/TDF or F/TAF. Among a cohort of persons prescribed F/TDF for PrEP by October 3, 2019 and with at least one PrEP prescription after that date, we assessed the proportion who switched to F/TAF. Using a multivariable Poisson regression model, we estimated the probability of switching from F/TDF to F/TAF vs. continuing on F/TDF for PrEP by patient demographic characteristics.

**Results:** The number of PrEP users prescribed F/TAF increased from 2,637 in the third quarter (Q3) of 2019 to 75,979 in the second quarter of 2020. The number of PrEP users prescribed F/TDF decreased starting in Q3 2019 (Figure). During October 1, 2019 to June 30, 2020, 43,316 (38.1%) of 113,559 new PrEP users were prescribed F/TAF. Among a cohort of 205,248 persons prescribed F/TDF before October 3, 2019 and with at least one PrEP prescription after that date, 57,059 (27.2%) switched to F/TAF. In a multivariable regression model, the adjusted probability of switching from F/TDF to F/TAF vs. continuing on F/TDF was higher in older persons (aRR 1.14, 95% CI 1.13- 1.15 for each 10 year age increase), persons privately insured vs. publicly insured (aRR 1.29, 95% CI 1.26 - 1.32), and persons living in the South vs. the Northeast (aRR 1.52, 95% CI 1.49 - 1.55).

**Conclusion:** Since approval of F/TAF in early October 2019, many PrEP users have initiated F/TAF or switched from F/TDF to F/TAF. As new patented and generic PrEP drugs become available, monitoring their use can help understand implications for U.S. healthcare system expenditures. Clinicians might consider prescribing less expensive options that can result in lower healthcare system expenditures for PrEP.

Figure. Persons prescribed PrEP from January 2014 to June 30, 2020 by type of PrEP drug, IQVIA Real-World Longitudinal Prescription database, United States



**697 WITHDRAWN**

**698 PrEP EFFICACY OVER THE FIRST 3 YEARS OF IMPLEMENTATION IN FRANCE: A NATIONWIDE STUDY**

**Marc-Florent Tassi**<sup>1</sup>, Emeline Laurent<sup>1</sup>, Guillaume Gras<sup>1</sup>, Lot Florence<sup>2</sup>, Francis Barin<sup>3</sup>, Karl Stefic<sup>3</sup>, Leslie Grammatico-Guillon<sup>1</sup>

<sup>1</sup>Centre Hospitalier Universitaire, Tours, France, <sup>2</sup>Santé Publique France, Saint-Maurice, France, <sup>3</sup>Institut National de la Santé et de la Recherche Médicale, Tours, France

**Background:** Oral pre-exposure prophylaxis (PrEP) is available since 2016 in France and was highly effective in clinical trials, decreasing HIV incidence to 0.19 per 100 person-years (95%-CI 0.01–1.08) among MSM users. HIV testing is recommended prior to PrEP initiation, one month after PrEP initiation and quarterly thereafter. This study aimed to assess the uptake of these guidelines and estimate the incidence of HIV infections among oral PrEP users, by developing an automated surveillance model using the French national health database (Système National des Données de Santé, SNDS).

**Methods:** Using SNDS database, a 3-year historic cohort study included every adult person covered by national health insurance who started an oral PrEP between January 1, 2016 and June 30, 2018. HIV infection was tracked in the follow-up, from the inclusion (1st PrEP dispensation) up to 2019, based on an algorithm including antiretroviral drug deliveries (out of tenofovir-emtricitabine association), laboratory tests for HIV diagnosis or monitoring (results not available), hospitalization data and HIV long-term chronic disease registration. Timelines leading to contamination were reviewed blindly by 2 HIV experts. Risk factors of low adherence to HIV testing in PrEP follow-up were analysed using a generalized linear mixed model.

**Results:** 9,893 PrEP users (99% males, median age 36 (IQR: 30–44) at PrEP initiation) were followed for a median duration of 546 days (IQR: 346–767) with a median of 9 PrEP dispensations (IQR: 4–14). The first HIV test at one month after PrEP initiation was performed by 70% of users. For subsequent tests, this rate exceeded 85% and remained stable over time. HIV testing was lower among PrEP users without prescription refill (OR 0.15, 99%-CI 0.12–0.20), but higher if the last prescription was made by a hospital practitioner (OR at 6 month 2.37, CI 1.88–3.01). After review, 29 HIV infections were identified (Cohen's kappa = 1) leading to an incidence of 0.19 case per 100 person-years (99%-CI 0.12–0.3). Infection may have occurred before or during PrEP initiation for 11 cases. For the 18 remaining cases the delay between last PrEP dispensation and diagnosis of HIV infection had a median duration of 180 days (IQR: 124–490).

**Conclusion:** In addition to clinical research, SNDS could be a powerful automated tool for optimizing PrEP monitoring and identifying risk factors of HIV infection. We confirmed the good follow-up and efficacy of PrEP in users, which should help decreasing HIV incidence in France.

**699 A NOVEL APPROACH TO MEASURE PrEP UPTAKE AMONG POPULATIONS WITH PERSISTENT HIV RISK**

**Preeti Pathela**<sup>1</sup>, Saba Qasmieh<sup>2</sup>, Monica Gandhi<sup>3</sup>, Elliot Rozen<sup>1</sup>, Harris Goldstein<sup>4</sup>, Hideaki Okochi<sup>3</sup>, Kelly Jamison<sup>1</sup>, Addie Crawley<sup>1</sup>, Joan Berman<sup>4</sup>, Betsy Herold<sup>4</sup>, Denis Nash<sup>2</sup>

<sup>1</sup>New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, <sup>2</sup>City University of New York, New York, NY, USA, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA, <sup>4</sup>Albert Einstein College of Medicine, Bronx, NY, USA

**Background:** Persons with sexually transmitted infections (STIs) are prime PrEP candidates, but the accuracy of using self-report to determine PrEP use is unknown. We used a novel approach to objectively measure PrEP use in a sentinel population largely representative of New York City (NYC) residents diagnosed with STIs, providing information about PrEP uptake and the accuracy of self-report.

**Methods:** We systematically accrued remnant serum samples from the following HIV-negative patients screened for syphilis at NYC Sexual Health Clinics (January-June 2019): men who have sex with men (MSM) and women with chlamydia (CT), gonorrhea (GC), and/or early syphilis (ES). Samples were tested for tenofovir/emtricitabine (detected vs. not detected) using a validated liquid chromatography-mass spectrometry (LC-MS) assay. Pairing test results with medical records, we assessed: 1) PrEP use on the day of STI diagnosis, 2) agreement of LC-MS assay with self-reported PrEP, and 3) correlates of PrEP use among MSM with rectal CT/GC or ES.

**Results:** PrEP use among 744 patients (331 MSM with rectal CT/GC, 122 MSM with ES, 85 MSM with urethral GC, 109 MSM with co-infections, 97 women

with GC/ES) was 32.8% (95% CI, 29.4%-36.3%). PrEP use was highest among White patients (45%) and MSM with ES (44%), and lowest among Black patients (20%) and women (2%). Agreement between LC-MS and self-reported PrEP use was 91%. Among MSM with rectal CT/GC or ES, PrEP use was associated with age [adjusted prevalence ratio (aPR)=1.6 (95% CI, 1.0-2.5) for ages 25-34 and aPR=2.0 (1.2-3.4) for ages 35-44, vs. 15-24 years]; number of recent sex partners [aPR=2.1 (1.3-3.4) for 6-10 partners and aPR=2.0 (1.2-3.3) for >10 partners, vs. <2 partners]; having sex/needle-sharing partners with HIV [aPR=1.4 (1.0-1.8)]; and inconsistently vs. always using condoms [aPR=3.1 (1.5-6.3)]. Race/ethnicity and past-year history of CT/GC/ES diagnoses or post-exposure prophylaxis were not associated.

**Conclusion:** This is the first study to analyze routinely collected remnant samples from STI clinics for a PrEP biomarker. Although the accuracy of self-reported PrEP was high, only 1 in 3 people with a newly diagnosed STI was on PrEP. PrEP use was associated with most measured HIV risk factors, but it is critical to increase use in racial minority populations and women. Surveillance studies using remnant samples can assess the accuracy of self-reported PrEP use in other settings and evaluate the success of interventions to increase PrEP uptake in high-risk populations.

## 700 PHARMACY REVERSALS: A NOVEL INDICATOR OF GAPS IN THE HIV PrEP CARE CASCADE

Lorraine T. Dean<sup>1</sup>, Hsien-Yen T. Chang<sup>1</sup>, William C. Goedel<sup>2</sup>, Philip Chan<sup>3</sup>, Jalpa A. Doshi<sup>4</sup>, Amy S. Nunn<sup>2</sup>

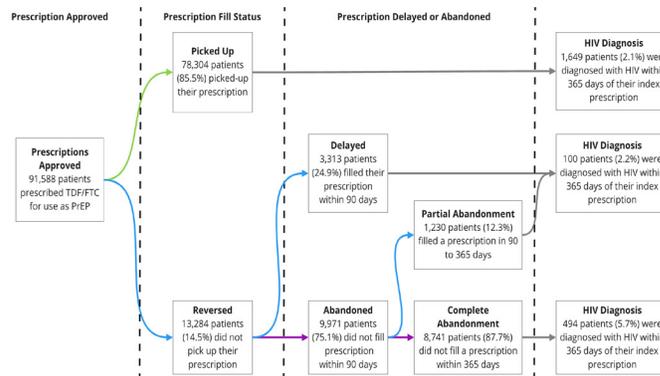
<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>Brown University, Providence, RI, USA, <sup>3</sup>The Miriam Hospital, Providence, RI, USA, <sup>4</sup>University of Pennsylvania, Philadelphia, PA, USA

**Background:** HIV PrEP retention in care is suboptimal with only 50-60% of patients retained in care at 12 months. Common biometric metrics for assessing PrEP persistence may be expensive, infeasible, or burdensome for patients to report in real-time. We introduce PrEP reversals, defined as when patients fail to pick up PrEP prescriptions, as a novel metric for population-based HIV PrEP persistence and a real-time indicator of gaps in the HIV care cascade.

**Methods:** We used a national claims database with up to 75% of all PrEP prescriptions in the United States. Data included claims from October 1, 2015 to September 30, 2019 across all public and private pharmacy types and across all US states. Patients were the unit of analysis. After using a multi-step process to identify HIV PrEP claims, we calculated the percentage of total index HIV PrEP insurer-approved prescription claims that were reversed (i.e. not picked up by the patient and claim withdrawn by the pharmacy). Among those with an initial reversal, we estimated the proportion who delayed (picked up within 90 days), partially abandoned (picked up between day 90 and day 365), or completely abandoned (reversed and not picked up within 365 days) their PrEP prescription over a 12-month period. For each metric, we calculated the percentage of PrEP patients who were later diagnosed with HIV.

**Results:** In our sample of 91,588 patients with 12-months of follow-up data, 14.5% had their index prescription reversed. Of these, 24.9% delayed initiation. Of those not picking up within 90 days, 12.3% filled PrEP between day 90 and day 365 whereas 87.3% did not fill any PrEP. Those who picked up after an initial reversal took an average of 194 days. Among those who completely abandoned their PrEP, 5.7% were diagnosed with HIV - nearly 3 times higher than those who picked up a prescription at some point.

**Conclusion:** Nearly 15% of patients do not pick up their PrEP from the pharmacy, and are at risk of being lost to PrEP care. Roughly two-thirds of patients who reversed their initial prescription ended up not picking up a prescription within 365 days, leaving them at greater risk of HIV. PrEP reversals give a national "lower bound" estimate of PrEP persistence using real-world and real-time data. This novel metric can be used for population-based surveillance, as a marker of those in need of HIV risk reduction intervention, or as an outcome for pharmacy-based interventions to improve PrEP persistence and reduce HIV risk.



## 701 LOW PROPORTIONS OF LINKAGE & PRESCRIPTIONS OF PrEP IN BLACK WOMEN (THRIVE, 2015-2020)

Ashley R. Townes<sup>1</sup>, Mary Tanner<sup>2</sup>, Kirk D. Henry<sup>2</sup>, Weiming Zhu<sup>2</sup>, Kashif Iqbal<sup>2</sup>, Kenneth L. Dominguez<sup>2</sup>, Karen W. Hoover<sup>2</sup>

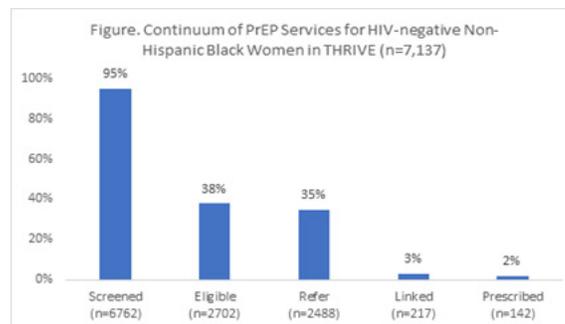
<sup>1</sup>Oak Ridge Institute for Science and Education, Atlanta, GA, USA, <sup>2</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** To reach the goal of ending the HIV epidemic in the United States, it is important to understand HIV prevention efforts for Black women who continue to be disproportionately affected by HIV, accounting for 58% of new HIV diagnoses among women in 2018. Although perceived behavioral risk is low in Black women, rates of bacterial sexually transmitted infections (STIs), such as syphilis and gonorrhea remain 4.7 times and 6.9 times the reported rate among White women. Those two bacterial STIs are indications for pre-exposure prophylaxis (PrEP), yet PrEP awareness and uptake remains low among Black women. The THRIVE demonstration project supported 7 U.S. health departments to provide comprehensive HIV prevention and care services to men who have sex with men of color but did not exclude other clients from receiving services.

**Methods:** We analyzed preliminary data collected from 8,648 non-Hispanic Black women enrolled in the THRIVE demonstration project. Data were reported by 7 project sites located in Alabama, Baltimore, Louisiana, New York City, Philadelphia, Virginia, and Washington DC from September 2015 through June 2020. We estimated the proportion of Black women aged ≥18 years who received HIV testing, STI screening, and PrEP services (e.g., screened, referred and linked to a PrEP provider, and prescribed PrEP) and calculated the positivity rates of syphilis, gonorrhea, and chlamydia.

**Results:** Among the 7,137 Black women in the THRIVE demonstration project who were HIV negative, 2,702 (38%) were eligible for PrEP and 2,488 (35%) were referred to a PrEP provider, yet only 217 (3%) were linked with a PrEP provider and 142 (2%) were prescribed PrEP medication (see Figure 1). Among all Black women in the sample, 69.8% were screened for bacterial STIs, including 62.9% for syphilis, 66.0% for gonorrhea, and 65.6% for chlamydia. The positivity of STI tests were 3.2% for syphilis, 4.6% for gonorrhea, and 4.8% for chlamydia.

**Conclusion:** Among Black women who were eligible, the proportions who were linked to a PrEP provider and prescribed PrEP were extremely low. In order to reach the goal of ending the HIV Epidemic in the United States, it is imperative that Black women have access to PrEP information and care. Programmatic activities focused on specifically meeting the HIV prevention needs of Black women are greatly needed.



**702 PrEP USE AND REFERRAL: BLACK PARTNERS OF PEOPLE WITH HIV IN PARTNER SERVICES, 2019**

**Shubha Rao<sup>1</sup>, Mesfin Mulatu<sup>1</sup>, Hui Zhang Kudon<sup>1</sup>, Wei Song<sup>1</sup>, Michele Rorie<sup>1</sup>**  
<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** Blacks or African Americans (hereafter Blacks) are disproportionately affected by Human Immunodeficiency Virus (HIV) in the United States. Effective prevention strategies must be scaled up in Black communities to achieve the national goal of reducing HIV-related disparities. HIV partner services (PS) provide an opportunity to link HIV-negative partners to prevention services, including pre-exposure prophylaxis (PrEP). However, the extent to which PrEP services are integrated into PS programs is not well known. This analysis examines current use of PrEP and referral to PrEP providers among HIV-negative Black partners contacted by PS programs at CDC-funded health departments.

**Methods:** In 2019, 48 of 60 health departments reported data on current PrEP use or referral to PrEP providers among HIV-negative partners of people with HIV (PWH). Of these, 20 reported PrEP data for ≥70% of HIV-negative partners and were used in this analysis. We conducted descriptive analysis to examine the pattern of current PrEP use and referral to PrEP providers among Black partners by age, gender, and U.S. census region. In addition, we conducted multivariate Poisson regression analyses to estimate the independent associations of age, gender, and U.S. census region with PrEP use and referral among Blacks. Adjusted prevalence ratios (aPR) and 95% confidence intervals (CI) were calculated.

**Results:** Partner services identified 710 HIV-negative Black partners of PWH. Of these, only 52 (7.3%) reported taking PrEP at the time of their contact with PS. There were no significant differences in prevalence of current PrEP use by age, gender, and geographic region. PS offered referral to 251 of 608 (41.3%) HIV-negative Black partners who were not on PrEP. There were no significant variations in PrEP referral by age and gender. However, Black partners residing in the South were less likely (14.7%; PR=0.25, 95% CI= 0.18–0.36) and those in Midwest more likely (70.4%; PR = 1.23, 95% CI = 1.03–1.47) than those in Northeast (55.4%) to have been referred to PrEP providers.

**Conclusion:** Less than one-half of Black partners of PWH contacted by PS were currently taking PrEP or referred to PrEP providers, suggesting continued risk for HIV infection. Low levels of PrEP use in general, and lower levels of PrEP referral in South indicate that PS programs need to identify and remove barriers to scale-up PrEP services among Blacks at risk for HIV infection

Table 1. Number and percent of Black partners of people with HIV who were on PrEP or referred to PrEP providers by demographic characteristics, 20 health departments, 2019

| Demographic Characteristics | Total HIV-Negative Partners* | On PrEP at Contact with Partner Services |                        | Total HIV-Negative Partners Not on PrEP** |                   | Referred to PrEP Providers by Partner Services |  |
|-----------------------------|------------------------------|--|------------------------|---|-------------------|--|--|
|                             |                              | n (Col. %)                               | n (Row %) aPR (95% CI) | n (Col. %)                                | n (Row %)         | aPR (95% CI)                                   |  |
| <b>Age</b>                  |                              |  |                        |   |                   |  |  |
| 13-29                       | 270 (38.0)                   | 28 (10.4)                                | Ref.                   | 223 (36.7)                                | 81 (36.3)         | Ref.   |  |
| 30-49                       | 288 (40.6)                   | 17 (5.9)                                 | 0.57 (0.32, 1.04)      | 253 (41.6)                                | 116 (45.8)        | 1.08 (0.89, 1.32)                              |  |
| ≥50                         | 83 (11.7)                    | 3 (3.6)                                  | 0.35 (0.11, 1.12)      | 68 (11.2)                                 | 30 (44.1)         | 1.16 (0.87, 1.56)                              |  |
| <b>Gender</b>               |                              |  |                        |   |                   |  |  |
| Male                        | 496 (69.9)                   | 36 (7.3)                                 | Ref.                   | 432 (71.1)                                | 179 (41.4)        | Ref.   |  |
| Female                      | 190 (26.8)                   | 12 (6.3)                                 | 0.92 (0.50, 1.70)      | 156 (25.7)                                | 67 (42.9)         | 1.01 (0.84, 1.21)                              |  |
| <b>Census Region</b>        |                              |  |                        |   |                   |  |  |
| Northeast                   | 256 (36.1)                   | 25 (9.8)                                 | Ref.                   | 195 (32.1)                                | 108 (55.4)        | Ref.   |  |
| Midwest                     | 119 (16.8)                   | 9 (7.6)                                  | 0.85 (0.40, 1.80)      | 108 (17.8)                                | 76 (70.4)         | 1.23 (1.03, 1.47) †                            |  |
| South                       | 259 (36.5)                   | 15 (5.8)                                 | 0.57 (0.30, 1.11)      | 232 (38.2)                                | 34 (14.7)         | 0.26 (0.18, 0.36) †                            |  |
| West                        | 76 (10.7)                    | 3 (3.9)                                  | 0.43 (0.14, 1.28)      | 73 (12.0)                                 | 33 (45.2)         | 0.79 (0.60, 1.04)                              |  |
| <b>Total</b>                | <b>710 (100.0)</b>           | <b>52 (7.3)</b>                          |                        | <b>608 (100.0)</b>                        | <b>251 (41.3)</b> |  |  |

Note: aPR = adjusted prevalence ratio; CI = confidence interval. PWH = people with HIV.

\*Data for partners with missing age 69 (9.7%) and gender 24 (3.4%) are not shown on the table.

\*\*Total number (n = 608) excludes HIV-negative partners already on PrEP (n=52; 7.3%) and those who had a missing value on the variable "Referred to PrEP Providers" (n=50; 7.0%). Data for partners with missing age (n=64; 10.5%) and gender (n=20; 3.3%) are not shown on the table.

† p < .001.

**703 PREEXPOSURE PROPHYLAXIS TRENDS BY HEALTH CENTER FEDERAL FUNDING STATUS, 2014-2019**

**Kirk D. Henny<sup>1</sup>, Weiming Zhu<sup>1</sup>, Patrick Schoen<sup>2</sup>, Ya-Lin A. Huang<sup>1</sup>, Lei Yu<sup>3</sup>, Suma Nair<sup>2</sup>, Karen W. Hoover<sup>1</sup>**

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>Health Resources and Services Administration, Rockville, MD, USA, <sup>3</sup>ICF International, Atlanta, GA, USA

**Background:** Expanding access to preexposure prophylaxis (PrEP) is an important strategy for achieving the goals of the Ending the HIV Epidemic initiative (EHE), particularly in high HIV burden urban areas. Federally Qualified Health Centers (FQHCs) and other healthcare settings serve a critical role in implementing HIV prevention strategies in EHE Phase I jurisdictions, where HIV diagnoses comprise more than half of annual HIV diagnoses. We assessed the trends in number of persons prescribed PrEP and the number of PrEP providers in the 48 EHE phase I urban jurisdictions.

**Methods:** We identified PrEP users and their PrEP providers in the IQVIA Real-World Longitudinal Prescription database during 2014-2019 using a previously validated algorithm. We identified all persons who were prescribed PrEP in EHE Phase I urban jurisdictions. Provider locations in the IQVIA database were cross-referenced with the Health Resources and Services Administration (HRSA) administrative and Uniform Data System data to distinguish between HRSA supported FQHC and non-FQHC providers. We estimated the annual numbers of PrEP users and PrEP providers among 877 HRSA supported FQHCs and 86,636 non-FQHC healthcare locations. We used a Poisson regression model to calculate the estimated annual percentage change (EAPC) and confidence intervals (CI) in the number of PrEP users and PrEP providers during the study period.

**Results:** The overall number of PrEP users in Phase I urban jurisdictions increased from 1,656 in 2014 to 27,479 in 2019 [EAPC 59.5, (95% CI 58.7, 60.3)]. The number of PrEP users in HRSA FQHCs [EAPC 101.5 (95% CI 97.6, 105.5)] increased more than in non-FQHCs [EAPC 56.2 (95% CI 55.4, 57.0)] (Table 1). The overall number of PrEP providers in Phase I urban jurisdictions increased from 586 in 2014 to 3,635 in 2019 [EAPC 38.4, (EAPC 95% CI 36.8, 40.0)]. The number of PrEP providers increased more in HRSA FQHCs [EAPC 49.1 (95% CI 41.9, 56.7)] compared to non-FQHCs [EAPC 37.8 (95% CI 36.2, 39.4)] (Table 1). Providers in HRSA FQHCs also had higher average PrEP patient per provider volume in 2019 [16.4 (95% CI 9.2, 23.5)] compared to those in non-FQHCs [7.0, (95% CI 6.2, 8.6)].

**Conclusion:** The growing numbers of PrEP users and providers highlight increasing access to and use of PrEP in EHE urban jurisdictions. The methods developed in our study can be used to evaluate local and national PrEP implementation activities in HRSA supported FQHCs in EHE jurisdictions.

Table 1. Number of preexposure prophylaxis users (PrEP) and PrEP providers in Ending the HIV Epidemic urban jurisdictions by HRSA supported Federally Qualified Health Center (FQHC) status, United States, 2014-2019

| Group                 | 2014  | 2015  | 2016  | 2017   | 2018   | 2019   | EAPC (95% CI)       | p-value |
|-----------------------|-------|-------|-------|--------|--------|--------|---------------------|---------|
| <b>PrEP Users</b>     |       |       |       |        |        |        |                     |         |
| FQHC                  | 81    | 263   | 439   | 870    | 1,932  | 3,625  | 101.5 (97.6, 105.5) | <.001   |
| non-FQHC              | 1,575 | 4,229 | 7,955 | 11,536 | 18,031 | 23,854 | 56.2 (55.4, 57.0)   | <.001   |
| <b>PrEP Providers</b> |       |       |       |        |        |        |                     |         |
| FQHC                  | 22    | 46    | 96    | 120    | 196    | 229    | 49.1 (41.9, 56.7)   | <.001   |
| non-FQHC              | 564   | 1,010 | 1,577 | 2,098  | 2,859  | 3,406  | 37.8 (36.2, 39.4)   | <.001   |

HRSA=Health Resources and Services Administration; EAPC=estimated annual percent change; CI=confidence interval

**704 OPTIMIZING HIV PREVENTION EFFORTS TO ACHIEVE EHE INCIDENCE TARGETS**

**Evin Jacobson<sup>1</sup>, Katherine A. Hicks<sup>2</sup>, Justin Carrico<sup>2</sup>, David Purcell<sup>1</sup>, Timothy Green<sup>1</sup>, Jonathan Mermin<sup>1</sup>, Paul Farnham<sup>1</sup>**

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>RTI Health Solutions, Research Triangle Park, NC, USA

**Background:** We optimized societal spending on HIV prevention (increased by given fixed amounts of federal funds) to assess whether it is possible to decrease annual HIV incidence in the United States to less than 10,000 cases in 5 years and less than 3,000 cases in 10 years, and thus achieve the HHS Ending the Epidemic (EHE) incidence targets.

**Methods:** We applied the HIV Optimization and Prevention Economics (HOPE) model, a dynamic, compartmental model that simulates that portion of the U.S. population aged ≥ 13 that is sexually active or injects drugs. Our analytic time horizon was 2020 through 2029. The model applied current estimated public and private HIV prevention spending (\$2.803 billion for 2020) each year to the following intervention categories: HIV screening (MSM and heterosexuals at

high and at low risk, and PWID), HIV care continuum (linkage to care at and after diagnosis, prescription of ART, retention in care, viral suppression), PrEP, and SSPs. To model the effect of additional prevention funding, we divided the 10-year time frame into three time periods and added \$500M/year for 2020–2021, \$1.5B/year for 2022–2024, and \$2.5B/year for 2025–2029. Using three scenarios, we estimated the impact of additional prevention and treatment spending with and without optimizing allocation of funds to the most impactful interventions: Scenario 1a with no optimization; Scenario 1b where the optimization started in year 6 of EHE period (2025, phase 2 of EHE); and Scenario 1c where the optimization started in year 3 of EHE period (2022).

**Results:** The additional prevention and treatment spending was approximately \$15B higher over the 10 year time period in all scenarios compared to the current allocation, and total infections decreased by around 190,000 to 240,000 in the three scenarios compared to the current allocation (Table: Scenario Comparisons). Only in Scenario 1c did the allocation of funds allow the 2024 and 2029 incidence targets to be met.

**Conclusion:** All three scenarios resulted in dramatic decreases in HIV incidence. However, optimization of prevention funding early in the time period was needed to reach EHE targets. An optimal allocation of resources is difficult to achieve in the real world, as it assumes flexibility of funding between various governmental and private agencies and programs to maximize efficacy of available funding. The EHE initiative has the potential for reaching ambitious goals with the dedication of significant funding increases across all 10 years of the initiative.

Table: Scenario Comparisons

|                    | Scenarios   | Current funding* | 1a <sup>1</sup> | 1b <sup>2</sup> | 1c <sup>3</sup> |
|--------------------|---|------------------|-----------------|-----------------|-----------------|
| 10-year cumulative | Incidence   | 363,494          | 176,757         | 156,982         | 123,613         |
|                    | Decrease in new infections compared to base                         |                  | 186,737         | 206,511         | 239,881         |
|                    | Prevention funding (\$M) **   | 28,030           | 46,030          | 46,030          | 46,030          |
|                    | Treatment spending (\$M) ***  | 333,347          | 332,572         | 330,123         | 326,034         |
|                    | Prevention and treatment spending (\$M)                             | 361,377          | 378,602         | 376,153         | 372,064         |
|                    | Additional prevention and treatment spending compared to base (\$M) |                  | 17,224          | 14,776          | 10,687          |
|                    | 2024 annual incidence (target 10k)                                  | 35,919           | 18,422          | 18,422          | 8,958           |
|                    | 2029 annual incidence (target 3k)                                   | 38,025           | 7,814           | 3,194           | 2,368           |

\* Annual societal HIV prevention funding: \$2.803B

\*\* Calculated by multiplying the total annual prevention funding by the number of years at that annual funding level for years 1 to 10.

\*\*\* Treatment spending, an outcome of the simulation, is dependent on the number of people on ART for each scenario.

<sup>1</sup> No optimization

<sup>2</sup> Optimization starting in year 6 (2025, phase 2 of EHE)

<sup>3</sup> Optimization starting in year 3 of EHE (2022)

\* Annual EHE funding: \$500M/year for 2020–2021; \$1.5B for 2022–2024; \$2.5B/year for 2025–2029

## 705 PREDICTORS OF PrEP UPTAKE IN A SEXUAL HEALTH CLINIC WITH IMMEDIATE PrEP INITIATION

Gabriel Wagner<sup>1</sup>, Kuan-Sheng Wu<sup>1</sup>, Alina Burgi<sup>1</sup>, Susan J. Little<sup>1</sup>

<sup>1</sup>University of California San Diego, San Diego, CA, USA

**Background:** Improved HIV pre-exposure prophylaxis (PrEP) uptake will be necessary for HIV eradication initiatives. Offering PrEP at the time of HIV testing can improve uptake by avoiding delays between HIV screening and initiation of PrEP typical in the traditional clinic setting. We instituted an immediate PrEP initiation program and assessed predictors of PrEP interest, initiation, and linkage.

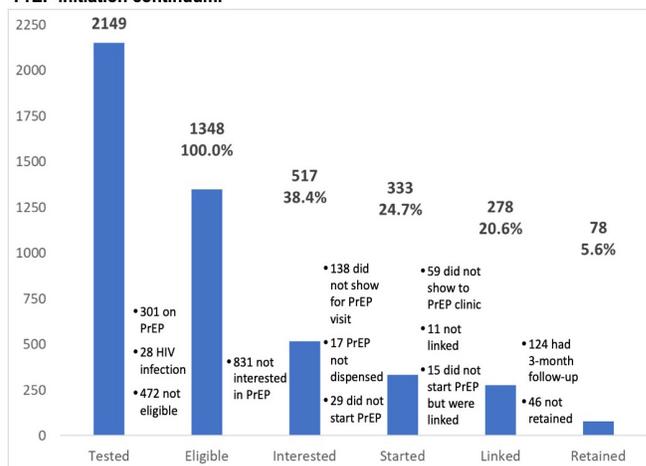
**Methods:** Between November 2018 and February 2020, PrEP-eligible individuals who presented to a community-based sexual health clinic in San Diego, California were assessed for interest in immediate PrEP initiation (I-PrEP). Interested individuals were referred to a study pharmacist to receive a free 30-day supply of PrEP as early as same day and within 7 days of HIV testing, and were also linked to a community PrEP care provider. Demographic, behavioral, and sexually transmitted infection (STI) data were collected. Univariable and multivariable analyses were conducted to determine predictors of PrEP interest, initiation, linkage, and retention in care at 3 months.

**Results:** Out of 2,149 individuals who presented for HIV/STI testing, 1,348 were eligible for PrEP, out of whom 517 (38.4%) were interested in starting PrEP and referred to the study pharmacist. Among those referred to the pharmacist, 333 (24.7%) actually started PrEP, 278 (20.6%) were linked to PrEP care, and, among those with follow-up, 78 (5.6%) remained in care at 3 months (Figure). Among predictors of multiple PrEP outcomes: testing positive for gonorrhea predicted

PrEP interest (aOR 2.44: 95%CI 1.48–4.02), initiation (aOR 5.00: 95%CI 2.20–11.39), and linkage (aOR 2.31: 95%CI 1.26–4.25). Non-Black race predicted both PrEP initiation (aOR Black 0.50: 95%CI 0.27–0.95) and linkage (aOR Black 0.32: 95%CI 0.16–0.64). Having private health insurance predicted both linkage (aOR 1.85: 95%CI 1.28–2.67) and retention (aOR 3.94: 95%CI 1.77–8.75).

**Conclusion:** Immediate PrEP initiation in a sexual health clinic was feasible, although only a minority of PrEP-eligible persons initiated PrEP and remained in care at 3 months. Having gonorrhea was a strong predictor of PrEP uptake. Being non-Black race and having private health insurance also predicted PrEP uptake, consistent with racial/ethnic and socioeconomic barriers to PrEP usage. Greater support is needed at each step of the PrEP initiation continuum to improve the implementation of similar programs.

Proportion of immediate PrEP (I-PrEP) study participants at each step of the PrEP initiation continuum.



## 706

## THE M-CUBED APP TO IMPROVE HIV PREVENTION AND CARE OUTCOMES IN MSM: RESULTS OF AN RCT

Patrick S. Sullivan<sup>1</sup>, Rob Stephenson<sup>2</sup>, Sabina Hirshfield<sup>3</sup>, Shelby Mullin<sup>1</sup>, Christina Mehta<sup>1</sup>, Ryan J. Zahn<sup>1</sup>, José A. Bauermeister<sup>4</sup>, Mary Ann Chiasson<sup>5</sup>, Martin Downing<sup>6</sup>, Deborah Gelaude<sup>7</sup>, Keith J. Horvath<sup>8</sup>, Eli Rosenberg<sup>9</sup>, Aaron J. Siegler<sup>1</sup>, Gordon Mansergh<sup>1</sup>, for the MMI Research Group  
<sup>1</sup>Emory University, Atlanta, GA, USA, <sup>2</sup>University of Michigan, Ann Arbor, MI, USA, <sup>3</sup>State University of New York Downstate Medical Center, Brooklyn, NY, USA, <sup>4</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>5</sup>Columbia University, New York, NY, USA, <sup>6</sup>City University of New York, New York, NY, USA, <sup>7</sup>US Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>8</sup>San Diego State University, San Diego, CA, USA, <sup>9</sup>State University of New York at Albany, Rensselaer, NY, USA

**Background:** Gay, bisexual and other men who have sex with men (GBMSM) face the highest burden of HIV in the United States, and there is a paucity of efficacious mobile health HIV prevention and care interventions tailored for diverse risk profiles of GBMSM. We developed and tested a mobile app (M-Cubed) that combined prevention messages and access to core prevention services among GBMSM in three US cities to promote key health services for HIV-negative MSM (HIV testing, STI testing, PrEP, condom use) and MSM living with HIV (HIV care, STI testing, condom use).

**Methods:** GBMSM (in three groups: lower-risk HIV-negative, higher-risk HIV-negative, and living with HIV) from Atlanta, Detroit, and New York City were enrolled in a randomized controlled trial to study the effects of the M-cubed prevention app on relevant HIV prevention and care outcomes, compared to a waitlist control. Men allocated to the intervention arm could access the M-cubed app for three months, including receipt of core and tailored prevention messages; ordering at-home HIV, at home STI test kits, and condoms; receiving PrEP eligibility screening and PrEP navigation; and access to service locators (HIV care, HIV testing, PrEP). The control arm was provided links to online health information. Self-reported prevention and care outcomes were collected by survey at baseline, immediately post-intervention, and at 3, 6, and 9 months post-intervention.

**Results:** 1220 GBMSM were enrolled, randomized and included in the intention to treat (ITT) analysis. For higher-risk GBMSM, allocation to the intervention arm was associated with a higher odds HIV testing in the prior three months at the immediate post-intervention assessment (aOR=2.02, 95% CI=1.11–3.66), and

with a higher odds of PrEP use at the 3-month post-intervention assessment (aOR=2.41, 95% CI=1.00-5.76), compared to control participants. No changes in HIV prevention or care outcomes were associated with allocation to the intervention arm for the lower-risk HIV-negative or living with HIV groups.

**Conclusion:** Access to the M-cubed app was associated with increased HIV testing and PrEP use among higher-risk HIV-negative GBMSM in three US cities. The app could be made available to communities for prevention implementation; additional implementation studies are needed to understand optimal strategies to implement the app outside of the research setting.

**707 RISK-BASED VS UNIVERSAL PrEP DELIVERY DURING PREGNANCY: A CLUSTER RANDOMIZED TRIAL**



**John Kinuthia**<sup>1</sup>, Julia Dettlinger<sup>2</sup>, Joshua Stern<sup>2</sup>, Nancy Mwangeli<sup>1</sup>, Laurén Gomez<sup>2</sup>, Felix Abuna<sup>1</sup>, Ben Ochieng<sup>1</sup>, Salphine Watoyi<sup>1</sup>, Mary Marwa<sup>1</sup>, Anjali Wagner<sup>2</sup>, Barbra A. Richardson<sup>2</sup>, Jillian Pintye<sup>2</sup>, Jared Baeten<sup>2</sup>, Grace John-Stewart<sup>2</sup>

<sup>1</sup>Kenyatta National Hospital, Nairobi, Kenya, <sup>2</sup>University of Washington, Seattle, WA, USA

**Background:** PrEP provision in maternal child health (MCH) clinics is important for women at risk for HIV acquisition during pregnancy. In high prevalence settings, the best strategies for PrEP delivery that balance benefits of HIV prevention against unnecessary PrEP exposure are unknown.

**Methods:** The PrEP Implementation for Mothers in Antenatal Care (PrIMA) cluster randomized trial compared two models of PrEP delivery in MCH clinics (NCT03070600). Twenty facilities in Siaya and Homa Bay, Kenya were randomized to either Targeted PrEP (HIV risk assessment via validated HIV risk score, and HIV self-test provision for partners, with PrEP offered to those with high-risk or if requested) versus Universal PrEP (standardized counseling and PrEP offer to all). The Targeted approach was hypothesized to improve risk perception and PrEP decision-making. Participants were enrolled during pregnancy and followed to 9 months postpartum. Primary outcomes were HIV incidence and 'appropriate PrEP use' (defined as PrEP used by women with high risk and not used by women with low risk per HIV risk score). PrEP was prescribed per national guidelines. Outcomes were compared between arms, clustered on facility and adjusted for baseline differences using generalized estimating equations.

**Results:** Between January 2018 and July 2019, 4,447 pregnant women were enrolled (2,197 Targeted, 2,250 Universal). Median age was 24 years (IQR 21, 28), most (85%) were married, and median gestational age was 24 weeks (IQR 20, 30). Overall, 1,877 (42%) were at risk for HIV acquisition at baseline, greater in the Targeted group (51% vs 33%, p<0.001). Retention at 9-months postpartum was 94% (92% Targeted, 96% Universal). PrEP was accepted by 18% of women in the Targeted arm versus 20% of women in the Universal arm (adjusted Risk Ratio (aRR) 0.6, 95% Confidence Interval (95% CI) 0.4-1.1). Appropriate PrEP use was 59% in the Targeted arm versus 68% in the Universal arm (aRR 1.1; 95% CI 0.8-1.6). Median duration of PrEP use was similar (8.9 vs 8.6 months, p=0.9). HIV incidence was 0.3 and 0.4/100 py (aRR 0.7, 95% CI 0.2-2.1).

**Conclusion:** At MCH sites in Kenya, a substantial proportion of pregnant women were at risk for HIV, used and continued PrEP, and maternal HIV incidence was low. Targeting by risk-based PrEP offer did not improve PrEP decision-making or decrease HIV incidence. Offering Universal PrEP counselling is an effective and efficient approach to achieve appropriate PrEP use among women at risk.

**Table 1: PrIMA study outcomes**

|   | n (%) or Median (IQR) |                   |                    |               |
|---|-----------------------|-------------------|--------------------|---------------|
|   | All subjects (N=4447) | Targeted (N=2197) | Universal (N=2250) | aRR (95% CI)  |
| Appropriate PrEP decision                     | 2838 (63.8)           | 1299 (59.1)       | 1539 (68.4)        | 1.1 (0.8-1.5) |
| HIV incidence (per 100 py) (95% CI)           | 0.3 (0.2-0.6)         | 0.3 (0.1-0.6)     | 0.4 (0.2-0.7)      | 0.7 (0.2-2.1) |
| PrEP acceptance                               | 828 (18.6)            | 387 (17.6)        | 441 (19.6)         | 0.6 (0.4-1.1) |
| Any PrEP use                                  | 723 (16.3)            | 326 (14.8)        | 397 (17.6)         | 0.6 (0.3-1.0) |
| Continued PrEP to 9 months postpartum (n=723) | 367 (51)              | 167 (51)          | 200 (50)           | --            |
| PrEP duration (months)                        | 8.8 (3.5, 11.6)       | 8.9 (3.7, 11.9)   | 8.6 (3.3, 11.4)    | p=0.9         |

**708 GLOBAL AND REGIONAL ESTIMATES OF THE CONTRIBUTION OF HSV-2 TO INCIDENT HIV INFECTIONS**

**Romain Silhol**<sup>1</sup>, Helen Coupland<sup>1</sup>, Rebecca Baggaley<sup>2</sup>, Lori Miller<sup>3</sup>, Lisa Staadegaard<sup>1</sup>, Sami Lynne Gottlieb<sup>4</sup>, James Stannah<sup>2</sup>, Katherine M. Turner<sup>6</sup>, Peter Vickerman<sup>6</sup>, Richard Hayes<sup>3</sup>, Philippe Mayaud<sup>3</sup>, Katharine J. Looker<sup>6</sup>, Marie-Claude Boily<sup>1</sup>

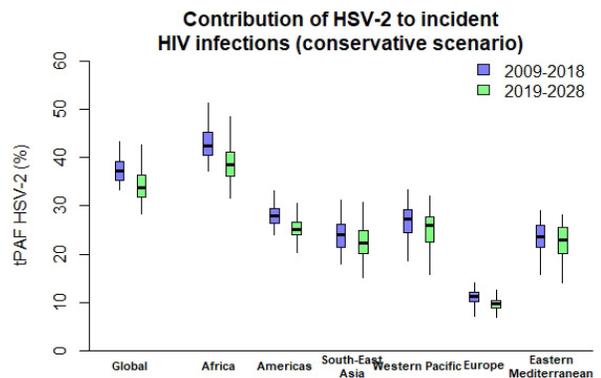
<sup>1</sup>Imperial College London, London, UK, <sup>2</sup>University of Leicester, Leicester, UK, <sup>3</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>4</sup>World Health Organization, Geneva, Switzerland, <sup>5</sup>McGill University, Montreal, Canada, <sup>6</sup>University of Bristol, Bristol, UK

**Background:** Evidence of biological interactions between herpes simplex virus type 2 (HSV-2) and HIV suggests that HSV-2 plays an important role in HIV epidemics. We improved previous estimates of the contribution of HSV-2 to incident HIV infections using a dynamic-transmission model accounting for direct/indirect transmissions (using population-attributable fractions (tPAFs)).

**Methods:** We developed a mathematical model of HSV-2/HIV transmission among 15-49-year-old heterosexual, non-drug injecting populations, calibrated to each of the six WHO regions using region-specific demographic and HSV-2/HIV epidemiological data. We derived global and regional estimates of the 10-year tPAF under three additive scenarios, assuming: (1) HSV-2 only increases HIV acquisition ("conservative" scenario), (2) HSV-2 increases HIV acquisition and transmission ("liberal"), (3) HIV/ART (antiretroviral therapy) also modifies HSV-2 transmission and HSV-2 decreases ART effect on HIV transmission ("fully liberal"). We compared predicted numbers of incident HIV infections (over 2009-2018) between each scenario and its counterfactual: no biological interactions.

**Results:** HSV-2/HIV biological interactions were necessary to reproduce empirical data on HIV incidence by HSV-2 status in Africa. Under the conservative scenario, our model predicted a tPAF of 37.3% (95% uncertainty interval 33.4-43.2%) and 5.6 (4.5-7.0) million incident heterosexual HIV infections due to HSV-2 globally over 2009-2018. The contribution of HSV-2 to incident HIV infections was largest for the African region (42.6% (38.0-51.2%) and 4.8 (3.6-6.5) million infections, respectively), and lowest for the European region (11.2% (7.9- 13.8%) and 0.11 (0.07-0.15) million) (Figure). The tPAF was higher among female sex workers, their clients, and older adults, reflecting their higher HSV-2 prevalence. Under the liberal scenario, the tPAF was 51.0% (42.7-58.2%) globally, 1.3-2.4-fold higher compared to the conservative scenario across regions. Accounting for additional modifying effects between HSV-2 and HIV/ART in the fully liberal scenario did not influence tPAF estimates, and tPAF did not substantially change when calculated over 2019-2028

**Conclusion:** Our results suggest that HSV-2 contributed to over a third of new HIV infections worldwide over 2009-2018 and will contribute similarly over 2019-2028. This was highest in Africa, despite increased ART access. Improved HSV-2 control measures, such as future vaccines could have a substantial impact on HIV incidence.



## 709 DAILY DOXYCYCLINE IN MSM ON PrEP FOR PREVENTION OF SEXUALLY TRANSMITTED INFECTIONS

Troy Grennan<sup>1</sup>, Mark Hull<sup>2</sup>, Saira Mohammed<sup>2</sup>, Tessa Tattersall<sup>1</sup>, Joshua Edward<sup>1</sup>, Amit Gupta<sup>1</sup>, Michelle K. Denney<sup>3</sup>, Marc Romney<sup>4</sup>, Muhammad Morshed<sup>1</sup>, Wendy Zhang<sup>2</sup>, Sidhant Guliani<sup>2</sup>, Jason Trigg<sup>2</sup>, Viviane D. Lima<sup>2</sup>, Julio S. Montaner<sup>2</sup>, Reka Gustafson<sup>1</sup>

<sup>1</sup>British Columbia Centre for Disease Control, Vancouver, Canada, <sup>2</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, <sup>3</sup>Ottawa Hospital Research Institute, Ottawa, Canada, <sup>4</sup>St Paul's Hospital, Vancouver, Canada

**Background:** MSM continue to experience high rates of sexually transmitted infections (STI). Use of HIV pre-exposure prophylaxis (PrEP) significantly reduces risk of HIV infection, and a similar strategy using daily doxycycline may serve as STI PrEP. We undertook a pilot study to determine STI outcomes of HIV-negative MSM on dual HIV/STI PrEP.

**Methods:** HIV-negative MSM with prior diagnosis of syphilis received 48 weeks of tenofovir DF 300mg-emtricitabine 200mg daily and were randomized 1:1 to receive either immediate daily doxycycline 100mg, or deferred doxycycline beginning 24 weeks later in an open-label pilot study of Dual Daily HIV and Syphilis PrEP (The DuDHS Study) in Vancouver, Canada. Participants underwent screening for STI every 3 months, with *Staphylococcus aureus* nares cultures collected to evaluate tetracycline/doxycycline resistance by Kirby Bauer testing. STI rates were compared between those on dual PrEP vs. HIV PrEP alone over the initial 24 weeks using Fishers Exact test.

**Results:** Fifty-two MSM were randomized with median age of 34 years (interquartile range [IQR], 29 – 43). Overall, 55.8% self-reported prior gonorrhea and chlamydia infection. Chlamydia infection occurred only in the deferred arm during the first 24 weeks (rate 0 vs. 81.63/100 PY,  $p = 0.001$ ), subsequently no infections occurred in either arm. No individuals in the immediate arm, and one individual in the deferred arm developed syphilis infection during the first 24 weeks (rate 0 vs. 8.16/100 PY,  $p = 0.98$ ) with no infections seen thereafter in either arm. By 24 weeks,  $n = 4$  in the immediate arm and  $n = 7$  in the deferred arm tested positive for gonorrhea (rate 31.37 vs. 57.14/100 PY,  $p = 0.505$ ), and only one additional infection was seen in each arm for 24 – 48 weeks. In a logistic model receipt of doxycycline was associated with reduced probability of any STI (OR 0.18, 95% CI 0.05 – 0.68) during the first 24 weeks. Tetracycline resistance was seen in 1/3 *S. aureus* isolates at 24 weeks and 3/6 isolates at 48 weeks in the immediate arm and in 1/2 isolates after six months of doxycycline use in the deferred arm.

**Conclusion:** STI PrEP using daily doxycycline demonstrated decreased rates of chlamydia infection while impact on syphilis could not be ascertained. Tetracycline resistance amongst nasal carriage of *S. aureus* was observed over the study duration. Further evaluation of potential benefits and antimicrobial resistance in a larger study may be warranted.

## 710 TENOFOVIR HAIR LEVELS SIMILAR AMONG PREGNANT AND POSTPARTUM PrEP USERS

Jillian Pintye<sup>1</sup>, Monica Gandhi<sup>2</sup>, John Kinuthia<sup>3</sup>, Felix Abuna<sup>4</sup>, Mary Marwa<sup>3</sup>, Salphine Watoyi<sup>3</sup>, Ben Ochieng<sup>3</sup>, Daniel Odinga<sup>3</sup>, Joshua Stern<sup>1</sup>, Laurén Gomez<sup>1</sup>, Nancy Mwongeli<sup>3</sup>, Hideaki Okochi<sup>2</sup>, Julia Dettlinger<sup>1</sup>, Grace John-Stewart<sup>1</sup>, Jared Baeten<sup>1</sup>

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA, <sup>3</sup>Kenya National Hospital, Nairobi, Kenya, <sup>4</sup>Kenya University, Nairobi, Kenya

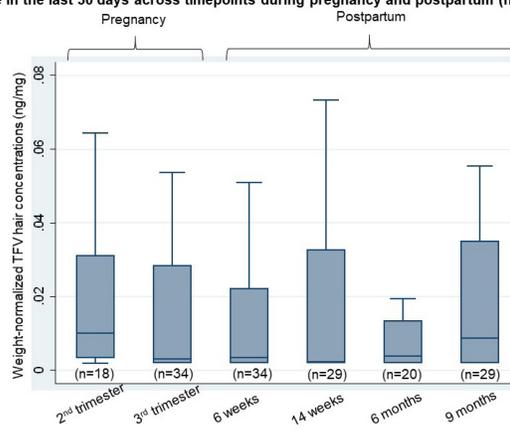
**Background:** Pregnancy may alter the pharmacokinetics (PK) of PrEP drugs in some biomatrices, with lower tenofovir (TFV) or metabolite concentrations in plasma and dried blood spots observed in pregnancy versus postpartum. Hair TFV levels measure cumulative exposure but have not been used to assess adherence among perinatal PrEP users to date. We measured TFV hair levels among Kenyan PrEP users, during pregnancy and postpartum.

**Methods:** PrEP Implementation for Mothers in Antenatal Care (PrIMA) is a cluster randomized trial in Kenya (NCT03070600) evaluating different PrEP counseling strategies for women in antenatal care. Women enrolled in PrIMA are followed through 9 months postpartum. Hair samples were collected at visits from a subset of women who reported using PrEP in the last 30 days. TFV hair levels in the distal 1 cm of hair (reflecting last 4 weeks of use) were analyzed by a validated liquid chromatography/tandem mass spectrometry assay. Correlates of weight-normalized TFV hair concentrations were identified via linear regression.

**Results:** In total, 164 hair samples were analyzed from 109 women. One-third (32%) of samples were from pregnancy visits and 68% were from postpartum visits. Median age of women was 27 years (IQR 23–34), 30% had partners known to be living with HIV, and median time on PrEP was 6 months (IQR 3–9) at sample collection. Median hair TFV concentration was 0.005 ng/mg (IQR 0.002–0.030) across pregnancy visits and 0.005 ng/mg (IQR 0.002–0.028) across postpartum visits and similar across timepoints (Figure 1). Overall, 29% of samples had TFV levels  $\geq 0.023$  ng/mg indicating  $\geq 4$  PrEP doses/week, according to benchmarks established in directly observed PK studies among non-pregnant participants; there was no difference pregnancy vs. postpartum in this benchmark (28% vs. 31%,  $p = 0.68$ ). Pregnancy status was not associated with TFV hair levels ( $p = 0.59$ ). Having a partner known to be living with HIV was associated with higher TFV levels in both pregnancy ( $p < 0.006$ ) and postpartum ( $p < 0.001$ ). Among women with TFV levels available both in pregnancy and postpartum ( $n = 28$ ), median TFV levels were 0.004 ng/mg (IQR 0.002–0.022) in pregnancy vs. 0.005 ng/mg (IQR 0.002–0.033) postpartum ( $p = 0.62$ ).

**Conclusion:** Our study shows that TFV levels in hair samples collected from PrEP users were comparable during pregnancy and postpartum. Hair metrics serve as cumulative measure of exposure and are unlikely to need adjustment for PK differences in the perinatal period when used as adherence metrics.

Figure 1. Tenofovir (TFV) hair concentrations among PrIMA participants who reported PrEP use in the last 30 days across timepoints during pregnancy and postpartum ( $n = 164$ )



## 711 THE IMPACT OF VIOLENCE ON PrEP ADHERENCE AMONG US CISGENDER WOMEN AT RISK FOR HIV

Katherine M. Anderson<sup>1</sup>, Jill Blumenthal<sup>1</sup>, Raphael J. Landovitz<sup>2</sup>, David J. Moore<sup>1</sup>, Katya Corado<sup>3</sup>, Richard H. Haubrich<sup>4</sup>, Ryan Kofron<sup>2</sup>, Sheldon Morris<sup>1</sup>, K. Rivet Amico<sup>5</sup>, Jamila K. Stockman<sup>1</sup>

<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>3</sup>Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA, <sup>4</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>5</sup>University of Michigan, Ann Arbor, MI, USA

**Background:** Violence is prevalent against women at-risk for HIV; survivors are at increased behavioral risk for HIV, while survivorship is linked to higher HIV susceptibility, via dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and female genital tract (FGT) microenvironment after physical or psychological trauma. Pre-exposure prophylaxis (PrEP) for HIV can mitigate this risk, but adherence remains challenging. We report findings on the impact of violence on PrEP adherence among at-risk cisgender women taking oral PrEP (daily tenofovir disoproxil fumarate/emtricitabine).

**Methods:** Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGIS) was an open-label clinical trial of PrEP adherence in cisgender women  $\geq 18$  years old at-risk for HIV in Southern California. Adherence was supported by two-way text messaging and counseling based on tenofovir diphosphate (TFV-DP) concentrations in dried blood spots. Participants completed a survey inclusive of violence history at weeks 0, 4, 12, 24, 36, and 48. TFV-DP concentrations consistent with  $\geq 4$  doses/week were considered to be "high adherence." Logistic regressions were used to assess odds of adherence.

**Results:** Of 136 participants, 38% were non-Hispanic Black, and 19% identified as Latina; mean age was 40 (SD:11). 22% ( $n = 29$ ) reported past year violence; 16% ( $n = 21$ ) reported physical and 15% ( $n = 20$ ) sexual violence. Sexual violence over lifetime was reported by 30% ( $n = 39$ ). Odds of high adherence at four weeks post-PrEP initiation are presented in Table 1; 50, or 43%, of participants

with available data were highly adherent at week 4. Odds of high adherence were lower among women with past year physical violence by 76% (aOR: 0.24, p=0.03), past year sexual violence by 75% (aOR: 0.25, p=0.04) and past year sexual or physical violence by 80% (aOR: 0.20, p<0.01), compared to non-exposed women. Participants with lifetime sexual violence had 73% lower odds of high adherence than those without (aOR: 0.27, p<0.01).

**Conclusion:** Cisgender women with experiences of violence have lower odds of having TFV-DP concentrations reflective of high or near-perfect adherence one-month post-initiation, compared to women not reporting violence. Providing support through comprehensive trauma services may improve both adherence and immune functioning. Given the prevalence of violence among women at-risk for HIV, PrEP programs should emphasize trauma screening and care in service delivery.

|                                       | OR   | 95% CI     | p     | aOR* | 95% CI     | p     |
|---------------------------------------|------|------------|-------|------|------------|-------|
| Adherence at ≥4 doses/week            |      |            |       |      |            |       |
| Past Year Physical Abuse              | 0.24 | 0.06, 0.90 | 0.03  | 0.24 | 0.06, 0.88 | 0.03  |
| Past Year Sexual Abuse                | 0.23 | 0.06, 0.85 | 0.03  | 0.25 | 0.07, 0.92 | 0.04  |
| Past Year Physical or Sexual Violence | 0.19 | 0.06, 0.61 | <0.01 | 0.20 | 0.06, 0.64 | <0.01 |
| Lifetime Sexual Abuse                 | 0.26 | 0.11, 0.65 | <0.01 | 0.27 | 0.11, 0.68 | <0.01 |

\*Adjusted for birth year, race, ethnicity, education, employment, and relationship status

**712 SEXUAL VIOLENCE AND PrEP USE AMONG MSM IN 23 US CITIES: NHBS, 2017**

**Jincong Freeman<sup>1</sup>, Johanna Chapin-Bardales<sup>1</sup>, Susan Cha<sup>1</sup>, Cyprian Wejnert<sup>1</sup>, Amy Baugher<sup>1</sup>,** for the NHBS Study Group, Division of HIV/AIDS Prevention  
<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** Men who have sex with men (MSM) who experience sexual violence (SV) are at increased risk for HIV. Pre-exposure prophylaxis (PrEP) is effective against HIV infection and can protect HIV-negative MSM experiencing SV from HIV acquisition. We estimated the percentage of PrEP use among MSM who reported experiencing SV in the past 12 months and examined the association between SV and PrEP use among MSM overall and by subgroups.

**Methods:** In 2017, National HIV Behavioral Surveillance (NHBS) used venue-based sampling to recruit and interview MSM in 23 U.S. cities. We analyzed data on key characteristics and SV experiences and PrEP use in the past 12 months among HIV-negative MSM. MSM with likely indications for PrEP included those who had either a male HIV-positive partner or ≥2 male partners and had either an STI or condomless anal sex with a male partner in the past 12 months. Weighted row percentages with 95% confidence intervals (CI) were reported. P-values were calculated using Rao-Scott chi-square tests.

**Results:** Overall, 7,121 HIV-negative MSM participated. Of these, 5.4% (95% CI: 4.6%-6.1%) reported experiencing SV in the past 12 months. MSM who reported experiencing SV were more likely to use PrEP compared to MSM who did not report experiencing SV (34.9% vs. 25.7%, p=0.008). A higher percentage of MSM who reported experiencing SV likely met the clinical indications for PrEP (82.7% vs. 77.3%, p=0.075). MSM who reported experiencing SV were more likely to use PrEP regardless of age group (18-29 years: 33.6% vs. 24.8%, p=0.037; 30 or older: 36.8% vs. 26.5%, p=0.048). Among white MSM, those who reported experiencing SV were more likely to use PrEP (44.0% vs. 31.7%, p=0.028). Among Hispanic/Latino or Black MSM, those who reported and who did not report experiencing SV had similar percentages of PrEP use (Hispanic/Latino: 29.4% vs. 21.8%, p=0.244; Black: 24.7% vs. 20.4%, p=0.478). MSM who reported experiencing SV were more likely to use PrEP regardless of health insurance coverage (insured: 37.2% vs. 28.7%, p=0.032; uninsured: 24.6% vs. 12.3%, p=0.040) or same-sex discrimination in healthcare (discriminated against: 55.8% vs. 29.1%, p=0.049; not discriminated against: 33.7% vs. 25.6%, p=0.020).

**Conclusion:** PrEP use was higher among MSM who experienced SV in the past 12 months overall and across multiple subgroups. MSM who experience SV may be more likely to need and initiate PrEP. Clinical SV screening may be an opportunity to identify HIV risk and PrEP needs and to assess MSM's safety.

Table 1. PrEP use in the past 12 months among MSM, by sexual violence and key characteristics – NHBS, 2017

| Characteristics  | Sexual violence     | Used PrEP in the past 12 months |                         | P-value <sup>†</sup> |
|--|---------------------|---------------------------------|-------------------------|----------------------|
|  |                     | n <sup>‡</sup>                  | Weighted row % (95% CI) |                      |
| <b>Overall</b>   | Yes                 | 147                             | 34.9 (27.9, 41.9)       | 0.008                |
|  | No                  | 1635                            | 25.7 (23.8, 27.6)       |                      |
| <b>Age (years)</b>                                       |                     |                                 |                         |                      |
| Young (18-29)  | Sexual violence Yes | 87                              | 33.6 (25.0, 42.3)       | 0.037                |
|  | No                  | 689                             | 24.8 (22.2, 27.3)       |                      |
| Older (≥30)  | Yes                 | 60                              | 36.8 (26.2, 47.3)       | 0.048                |
|  | No                  | 946                             | 26.5 (23.9, 29.0)       |                      |
| <b>Race/Ethnicity<sup>§</sup></b>                        |                     |                                 |                         |                      |
| Hispanic/Latino  | Sexual violence Yes | 27                              | 29.4 (15.5, 43.3)       | 0.244                |
|  | No                  | 398                             | 21.8 (18.9, 24.6)       |                      |
| Black  | Yes                 | 29                              | 24.7 (12.0, 37.5)       | 0.478                |
|  | No                  | 286                             | 20.4 (17.2, 23.7)       |                      |
| White  | Yes                 | 72                              | 44.0 (32.9, 55.1)       | 0.028                |
|  | No                  | 784                             | 31.7 (28.5, 34.9)       |                      |
| <b>Currently has health insurance</b>                    |                     |                                 |                         |                      |
| Yes  | Sexual violence Yes | 131                             | 37.2 (29.3, 45.0)       | 0.032                |
|  | No                  | 1473                            | 28.7 (26.5, 30.9)       |                      |
| No   | Yes                 | 16                              | 24.6 (9.9, 39.2)        | 0.040                |
|  | No                  | 161                             | 12.3 (9.5, 15.1)        |                      |
| <b>Same-sex discrimination in healthcare<sup>¶</sup></b> |                     |                                 |                         |                      |
| Yes  | Sexual violence Yes | 13                              | 55.8 (29.0, 82.6)       | 0.049                |
|  | No                  | 53                              | 29.1 (18.7, 39.5)       |                      |
| No   | Yes                 | 134                             | 33.7 (26.7, 40.8)       | 0.020                |
|  | No                  | 1580                            | 25.6 (23.7, 27.6)       |                      |

Abbreviations: PrEP = Pre-exposure prophylaxis; MSM = Men who have sex with men; NHBS = National HIV Behavioral Surveillance.

<sup>†</sup>Frequencies are unweighted and row percentages are weighted.

<sup>‡</sup>P-values are based on Rao-Scott chi-square tests.

<sup>§</sup>Hispanic/Latinos can be of any race. Racial groups that had coefficients of variation (CVs) >0.3 were not reported.

<sup>¶</sup>Participants were asked if they were denied or given lower quality health care because someone knew or assumed they were attracted to men.

**713 PREDICTORS OF PrEP ADHERENCE AND RETENTION IN US CISGENDER WOMEN AT RISK FOR HIV**

**Jill Blumenthal<sup>1</sup>, Sonia Jain<sup>2</sup>, Feng He<sup>1</sup>, K. Rivet Amico<sup>3</sup>, Jamila K. Stockman<sup>1</sup>, Ryan Kofron<sup>4</sup>, Christina Psaros<sup>5</sup>, Katya Corado<sup>6</sup>, Richard H. Haubrich<sup>7</sup>, Peter Anderson<sup>8</sup>, David J. Moore<sup>2</sup>, Raphael J. Landovitz<sup>4</sup>, Sheldon Morris<sup>2</sup>**

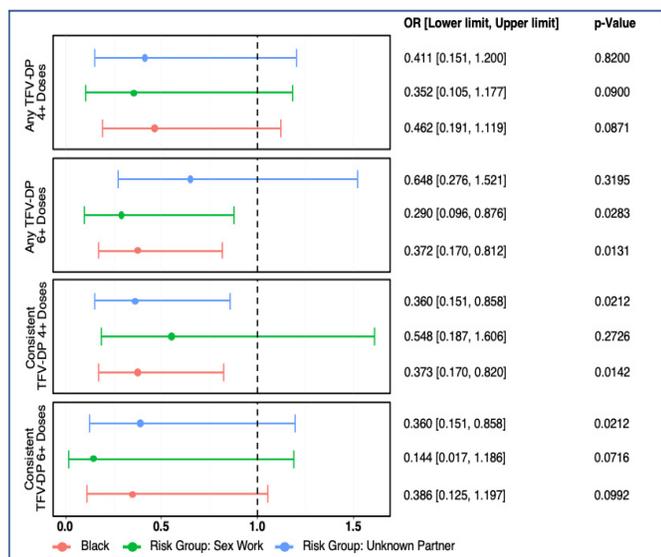
<sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>University of California San Diego, San Diego, CA, USA, <sup>3</sup>University of Michigan, Ann Arbor, MI, USA, <sup>4</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>5</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>6</sup>Harbor-UCLA Medical Center, Torrance, CA, USA, <sup>7</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>8</sup>University of Colorado, Aurora, CO, USA

**Background:** HIV pre-exposure prophylaxis (PrEP) effectiveness depends on adherence, which requires retention in PrEP care. We examined factors associated with PrEP adherence and retention among at-risk cisgender women prescribed oral PrEP.

**Methods:** Adherence Enhancement Guided by Individualized Texting and Drug Levels (AEGiS) was a 48-week single-arm open-label demonstration study of daily oral tenofovir disoproxil fumarate/emtricitabine in cisgender women ≥18 years old at risk for HIV conducted at five Southern California sites. Study visits occurred at baseline and at weeks 4, 12, 24, 36 and 48. Adherence was supported with text messages and titrated adherence counseling based on rapid-turnaround tenofovir diphosphate (TFV-DP) concentrations from dried blood spots. Adherence was examined in four ways: (a) having any TFV-DP ≥4 doses per week (d/w), (b) having any TFV-DP ≥6 d/w, (c) having all TFV-DP ≥4 d/w, and (d) having all TFV-DP ≥6 d/w at all visits attended. Retention was defined as completing the week 48 visit. We used univariate and multivariable logistic regression to identify baseline demographic and sociobehavioral predictors associated with adherence and retention.

**Results:** From June 2016 to October 2018, 136 cisgender women enrolled [mean age 40yo (SD 11); 38% non-Hispanic Black and 19% Latina]. In univariate analyses, cisgender Black vs non-Black women (58%, 30%, p=0.003), those attending LA vs San Diego site (79%, 58%, p=0.017) and those having partners of unknown risk vs a partner living with HIV (48%, 25%, p=0.012) were less likely to have consistent TFV-DP ≥4 d/w (findings similar for consistent TFV-DP 6 d/w). However, only Black race (OR 0.37, p=0.014) and having partners of unknown risk (OR 0.36, p=0.02) with all TFV-DP ≥4 d/w remained significantly associated in the multivariable analysis (see Forest Plot for all adherence outcomes). In univariate analyses, severe drug abuse on the DAST-10 (19%, 5%, p=0.031) was associated with lower likelihood of retention and interest in becoming pregnant in the next 6 months (13%, 32%, p=0.03) with greater likelihood of retention. Only pregnancy interest remained significant in multivariable models (OR 2.81, p=0.042).

**Conclusion:** In this cohort of cisgender women on PrEP, race and HIV risk group affected adherence whereas severe drug use negatively, and desire to become pregnant positively, impacted retention. Larger prospective studies should evaluate factors associated with long-term adherence and engagement in real-world PrEP settings.



**714 WEEKLY ORAL TENOFOVIR ALAFENAMIDE PROTECTS MACAQUES FROM VAGINAL SHIV INFECTION**

**Ivana Massud<sup>1</sup>**, Kenji Nishiura<sup>1</sup>, Susan Ruone<sup>1</sup>, Angela Holder<sup>1</sup>, Chuong Dinh<sup>1</sup>, Shanon Ellis<sup>1</sup>, Kristen Kelley<sup>1</sup>, George Khalil<sup>1</sup>, Walid Heneine<sup>1</sup>, Gerardo Garcia-Lerma<sup>1</sup>, Charles Dobard<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** Poor adherence to daily pre-exposure prophylaxis (PrEP) reduces efficacy and public health benefit. Simpler oral regimens providing long-lasting protection for one or more weeks may be more desirable among people who have difficulties adhering to a daily pill. Here, we report the pharmacokinetic (PK) assessment of a weekly oral tenofovir alafenamide (TAF) regimen in pigtailed macaques and its efficacy against vaginal SHIV infection.

**Methods:** We previously defined the human equivalent dose of oral TAF and TDF in macaques to be 1.5 and 22 mg/kg, respectively. Here we assessed in macaques the PK profile of a higher dose of TAF (27.4 mg/kg) in plasma and PBMCs following a single oral dose. Efficacy was determined in macaques that received a weekly 27.4 mg/kg dose of oral TAF and were vaginally exposed to SHIV162p3 at 3- and 6-days post dosing for up to 6 weeks (12 challenges). Infection outcome was compared to 10 untreated macaques. Tenofovir (TFV) and TFV diphosphate (TFV-DP) were measured by LC-MS/MS. SHIV RNA was monitored weekly in plasma by RT-PCR.

**Results:** Median TFV levels in plasma at 5h were 284 ng/ml (range 227-341). TFV-DP levels in PBMCs (fmols/10<sup>6</sup> cells) were 14,090, 6,740, and 4,390 at 5h, 3 days, and 6 days, respectively. Nine of 10 untreated controls were infected after a median of 3 SHIV exposures (range 1-12). In contrast, 5/6 animals receiving a single dose of oral TAF were protected against vaginal SHIV infection (Efficacy = 92.1% [95%CI=39.6%, 99.0%]). Median TFV-DP levels in the protected animals at time of challenge (day 3 and 6) were 6,095 and 3,485 fmols/10<sup>6</sup> cells, respectively. In contrast, the PrEP breakthrough animal showed much lower TFV-DP in PBMCs at challenges prior to infection (median = 405 [274-677] fmols/10<sup>6</sup> cells). Using in vivo C<sub>max</sub> TFV-DP levels and calculated TFV-DP half-life in PBMCs of 5.3 days, we estimate the length of prophylactic window will extend well beyond 1 week.

**Conclusion:** We identified a dose of oral TAF that resulted in high and sustained TFV-DP levels in PBMCs and protected against vaginal SHIV infection for at least 1 week following a single oral administration. The data open the possibility for long-lasting PrEP protection with infrequent oral dosing.

**715 PHARMACOKINETICS OF TAF/EVG RECTAL INSERTS IN MACAQUES AND IMPACT OF RECTAL WASH**

**Natalia Makarova<sup>1</sup>**, Tyana Singletary<sup>1</sup>, M M. Peet<sup>2</sup>, James Mitchell<sup>1</sup>, Angela Holder<sup>1</sup>, Chuong Dinh<sup>1</sup>, Walid Heneine<sup>1</sup>, Gerardo Garcia-Lerma<sup>1</sup>, Meredith Clark<sup>3</sup>, James Smith<sup>1</sup>, Gustavo Doncel<sup>3</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>CONRAD, Arlington, VA, USA, <sup>3</sup>Eastern Virginia Medical School, Norfolk, VA, USA

**Background:** On-demand topical products for HIV prevention may have several advantages, including limited cost and systemic toxicity. CONRAD has developed inserts containing tenofovir alafenamide fumarate (TAF) and elvitegravir (EVG) for on-demand vaginal or rectal pericoital use. We recently showed that TAF/EVG inserts provided high protection as PrEP or PEP in pigtail macaques exposed vaginally to simian HIV (SHIV). Here, we assessed the PK of the same inserts when applied rectally in pigtailed macaques. Since rectal cleansing is a common practice among men who have sex with men, we also defined the impact of rectal cleansing on drug distribution through the rectum and colon.

**Methods:** Six female pigtailed macaques received a single insert containing 20 mg of TAF and 16 mg of EVG at 4 cm from the anal margin. Rectal biopsies (Bx), rectal secretions, and blood were longitudinally collected at 0, 2, 4, 24, 120, and 168 hours post-application. Drug biodistribution and feces' interference were evaluated in 5 additional SHIV positive animals at necropsy. Of these 5 animals, three received rectal washes before dosing. Necropsy was done 4 hours post-dosing, with Bx collection at 4, 8, 15 (rectum) and 25 cm (colon) from the anal margin. Levels of TFV-DP and TAF/TFV/EVG in tissues and secretions were measured by LC-MS/MS.

**Results:** In the longitudinal PK study, TFV -DP levels in rectal tissues peaked at 4 hours (median 2187; range 411-2500 fmol/mg tissue), remaining detectable up to 7 days after dosing. EVG also peaked at 4 hours in tissues with a median 8.1 x 10<sup>3</sup> and was detectable until day 5. TAF was not detected in rectal fluids or tissues. Analysis of drug biodistribution in the rectum and colon at necropsy demonstrated a linear decline in levels of EVG and TFV-DP from 4 to 25 cm (Table 1). Rectal cleansing before insert application increased concentrations of TFV-DP and EVG in the rectum and colon by 40 to 200 times (Table 1).

**Conclusion:** Rectal application of TAF/EVG inserts resulted in tissue EVG and TFV-DP levels at 4 hours that were high and within the range of those associated with vaginal protection. Rectal wash was associated with extended biodistribution of TFV-DP and EVG throughout the rectum and increased tissue drug levels by several orders of magnitude. SHIV challenge studies will help define the rectal protection achieved with TAF/EVG inserts.

**Table 1. Median drug concentration in rectal biopsies**

| Cleansing    | TFV ng/g |        | TFV-DP (fmol/mg) |       | EVG (ng/g) |       |
|--------------|----------|--------|------------------|-------|------------|-------|
|              | w/o      | with   | w/o              | with  | w/o        | with  |
| Rectum 4 cm  | 125618   | 137903 | 1976             | 27858 | 988        | 33311 |
| Rectum 8 cm  | 46754    | 68567  | 1125             | 12300 | 385        | 18131 |
| Rectum 12 cm | 36753    | 26988  | 71               | 5629  | 805        | 3128  |
| Colon        | 2288     | 38712  | BLQ              | 4825  | BLQ        | 3509  |

**716 ACCEPTABILITY AND CHOICE FOR 3 PLACEBO PRODUCTS USED WITH RECEPTIVE ANAL SEX**

**José A. Bauermeister<sup>1</sup>**, Ryan Tingler<sup>1</sup>, Albert Liu<sup>2</sup>, Suwat Chariyalertsak<sup>3</sup>, Craig Hoesley<sup>4</sup>, Pedro Gonzales<sup>5</sup>, Ken Ho<sup>6</sup>, Noel Kayange<sup>7</sup>, Thesla Palanee-Phillips<sup>8</sup>, Sherri Johnson<sup>9</sup>, Jillian Zemanek<sup>10</sup>, Cindy Jacobson<sup>11</sup>, Gustavo Doncel<sup>12</sup>, for the MTN-035 Protocol Team for the Microbicide Trials Network

<sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>San Francisco Department of Public Health, San Francisco, CA, USA, <sup>3</sup>Chiang Mai University, Chiang Mai, Thailand, <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA, <sup>5</sup>IMPACTA, San Miguel, Peru, <sup>6</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>7</sup>Johns Hopkins University Research Project, Blantyre, Malawi, <sup>8</sup>Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, <sup>9</sup>FHI 360, Washington, DC, USA, <sup>10</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>11</sup>Magee-Womens Research Institute, Pittsburgh, PA, USA, <sup>12</sup>Eastern Virginia Medical School, Norfolk, VA, USA

**Background:** End-user perspectives are vital to the design of new biomedical HIV prevention products. Behaviorally congruent alternatives to condoms and daily oral Pre-Exposure Prophylaxis (PrEP) remain crucial. MTN-035 evaluated the acceptability of and preference for three placebo, non-gel delivery vehicles (insert, enema, suppository) that could be used to deliver PrEP prior to receptive anal sex (RAS).

**Methods:** We enrolled 217 HIV-negative, cisgender men who have sex with men (MSM) and transgender people ages 18–35 into a randomized cross-over trial across 7 sites in the United States, Peru, Malawi, South Africa, and Thailand. Participants were asked to use each product prior to RAS over 4-week periods. At the final study visit, product-experienced participants completed a conjoint experiment where they selected between random sets of product profiles using 7 features (delivery vehicle, timing of use before sex, side-effects, duration of protection, efficacy, frequency of use, and need for a prescription). A subset of participants completed an exit in-depth-interview (IDI; n=70).

**Results:** Participants identified as cisgender men (172; 79.3%), transwomen (42; 19.4%) or transmen (3; 1.3%). Mean age was 24.8 (SD=4.7 years). Product-experienced participants had heterogeneity in top-ranked product choices across scenarios (Table 1). In conjoint analyses, efficacy was the strongest determinant of stated choice overall (30.4%), followed by product delivery vehicle (18.0%), and side-effects (17.2%). The most common chosen combination of attributes was an enema used ~ 30 minutes before sex, with 95% efficacy, offering a 3-5 day protection window, used weekly, having no side effects, and available as an over-the-counter product. In IDIs, participants' acceptability across products were informed by the aforementioned features, RAS-related characteristics (e.g., lubricity; hygiene), personal considerations (e.g., relationship status), and social context (e.g., stigma).

**Conclusion:** Choice in next generation PrEP products, informed by acceptability and personal preference, is highly desired by MSM and transgender people. MTN-035 participants weighed product features differently, recognizing the potential to create diverse, behaviorally congruent biomedical options that fit the needs of intended end-users. Rather than one-size fits all, our findings underscore the variations in acceptability of non-gel delivery vehicles for local biomedical prevention prior to RAS.

**Table 1.** Product-Experienced Participants' Top Ranked Product Choice Based on Behavioral and Product-Related Characteristics

|   | Most Preferred Product                           |
|---|--|
| The product is a good alternative to lube.  | Suppository (42%)<br>Enema (38%)<br>Insert (20%) |
| It is easy to use the product every time you have sex.  | Enema (44%)<br>Insert (33%)<br>Suppository (23%) |
| It is easy to store the product discreetly.   | Insert (56%)<br>Suppository (31%)<br>Enema (13%) |
| It is easy to use the product before sex.   | Enema (47%)<br>Insert (29%)<br>Suppository (24%) |
| The product makes you feel clean after its use.   | Enema (78%)<br>Suppository (12%)<br>Insert (10%) |
| The product makes sex feel more pleasurable.  | Enema (59%)<br>Suppository (23%)<br>Insert (18%) |
| Fits your lifestyle if it provided some protection against HIV transmission when used before sex. | Enema (49%)<br>Insert (29%)<br>Suppository (22%) |

## 717 LONG-ACTING HIV CAPSID INHIBITOR EFFECTIVE AS PrEP IN A SHIV RHESUS MACAQUE MODEL

**Elena Bekerman**<sup>1</sup>, Samuel J. Vidal<sup>2</sup>, Derek Hansen<sup>1</sup>, Bing Lu<sup>1</sup>, Kelly Wang<sup>1</sup>, Abishek Chandrashekar<sup>2</sup>, Jim Zheng<sup>1</sup>, William Rowe<sup>1</sup>, Darryl Kato<sup>1</sup>, Christian Callebaut<sup>1</sup>, Wade Blair<sup>1</sup>, Tomas Cihlar<sup>1</sup>, Stephen Yant<sup>1</sup>, Romas Gelezunas<sup>1</sup>, Dan Barouch<sup>2</sup>

<sup>1</sup>Gilead Sciences, Inc, Foster City, CA, USA, <sup>2</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA

**Background:** The ability of daily oral preexposure prophylaxis (PrEP) to effectively reduce the risk of contracting HIV is strongly dependent on high medication adherence, which is not uniformly achieved among people at risk for HIV. Long-acting agents can circumvent the need for daily dosing while providing long-term protection. Lenacapavir (LEN), an investigational small molecule inhibitor of HIV capsid function with picomolar antiviral potency and long-acting subcutaneous (s.c.) dosing potential (twice yearly), is in clinical development for HIV treatment. Here, we evaluated GS-CA1, a LEN analog active against both HIV and SIV, as a long-acting PrEP agent in a macaque rectal SHIV challenge model.

**Methods:** Eight naïve Indian rhesus macaques per group received a single s.c. injection of either vehicle control (placebo), 150 mg/kg (low dose) or 300 mg/kg (high dose) GS-CA1, followed by weekly escalating titer SHIV challenges starting 1-week post-dosing. Blood was collected weekly for the evaluation of plasma drug levels, viral loads, and serology. Animals were considered protected if they remained SHIV-negative by plasma PCR assay and seronegative by enzyme immunoassay throughout the 15-week challenge phase and the 10-week follow-up.

**Results:** Following a single injection, plasma concentrations of GS-CA1 exceeded its serum protein binding adjusted (pa) EC95 value (30.1 nM) for 8-15 weeks and 15-17 weeks in the low and high dose groups, respectively. After a total of 15 challenges 8/8 animals became infected in the placebo group, whereas 2/8 and 5/8 animals remained protected in the low and high GS-CA1 dose groups, respectively. The median time-to-infection was 7.5 weeks in the placebo group, 16 weeks in the low-dose GS-CA1 group, and not reached due to insufficient number of infections in the high-dose group. Relative to the placebo group, the low and high dose treatment groups demonstrated an 86% (p=0.0061) and 96% (p=0.0002) infection risk reduction, respectively, as determined by Cox regression analysis. Notably, based on a 2-week infection-to-detection window, treatment group infections occurred only after plasma GS-CA1 concentrations fell below 2X paEC95.

**Conclusion:** These preclinical data provide a proof of concept for the prophylactic efficacy of a long-acting capsid inhibitor in a nonhuman primate SHIV challenge model and support the clinical development of LEN for HIV prevention.

718

## INFUSION REACTIONS IN THE PHASE 2B ANTIBODY MEDIATED PREVENTION (AMP) STUDIES

**Simbarashe Takuva**<sup>1</sup>, Shelly Karuna<sup>1</sup>, Michal Juraska<sup>1</sup>, Erika Rudnicki<sup>1</sup>, Srilatha Edupuganti<sup>2</sup>, Maija Anderson<sup>1</sup>, Robert De La Grecca<sup>1</sup>, Martin R. Gaudinski<sup>3</sup>, Margarita M. Gomez Lorenzo<sup>3</sup>, David Burns<sup>3</sup>, Myron S. Cohen<sup>4</sup>, Lawrence Corey<sup>1</sup>, Kathy Mngadi<sup>5</sup>, Nyaradzo M. Mgodhi<sup>6</sup>, for the AMP Study Teams

<sup>1</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>2</sup>Emory University, Atlanta, GA, USA, <sup>3</sup>National Institutes of Health, Bethesda, MD, USA, <sup>4</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>5</sup>Aurum Institute, Johannesburg, South Africa, <sup>6</sup>University of Zimbabwe, Harare, Zimbabwe

**Background:** The AMP studies, HVTN 703/HPTN 081 and HVTN 704/HPTN 085, two harmonized phase 2b, randomized, double-blind, placebo-controlled trials, assessed the safety and efficacy of infusion of the broadly neutralizing monoclonal antibody (mAb) VRC01 to prevent HIV acquisition. Infusion related reactions (IRRs) are commonly observed with murine or chimeric mAbs in oncologic and anti-inflammatory applications, but have not been comprehensively described for fully human, anti-viral mAbs.

**Methods:** Men who have sex with men and transgender individuals at risk for HIV (n=2699) enrolled in Brazil, Peru, Switzerland, and the US (704/085). At-risk, sexually active heterosexual women (n=1924) enrolled in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe (703/081). From April 2016 to April 2020, participants were randomized 1:1 to receive intravenous VRC01 at 10 mg/kg, 30 mg/kg, or placebo. In 704/085, 23,867 infusions were administered; in 703/081, 16,807 infusions were administered. Infusions were given about every 8 weeks, for 10 infusions total over 72 weeks. Safety was assessed immediately pre- and post-infusion and at monthly follow-up visits.

**Results:** Forty-seven (1.7%) participants experienced 49 IRRs in 704/085 and 93 (4.8%) experienced 111 IRRs in 703/081 (p<0.01 for a difference by trial). Four IRR clinical phenotypes were observed: urticaria, dyspnea, dyspnea with rash, and "other" reactions including pruritis and flushing. Urticaria was the most prevalent phenotype, occurring in 25 (0.9%) and 41 (2.1%) 704/085 and 703/081 participants, respectively; observed more frequently in VRC01 than placebo recipients (92.3% of urticarias in 704/085, 95.1% of urticarias in 703/081); and suggesting a dose-response trend across treatment groups in both trials. In total, 16 participants experienced between two to four IRRs. Most IRRs occurred with the initial infusion (36.7% in 704/085, 30.6% in 703/081). IRRs occurred more frequently in VRC01 than placebo recipients in 703/081 (p<0.01), though not in 704/085 (p=0.75). IRRs were associated with atopy in both trials (p=0.01 in 704/085, p<0.01 in 703/081) and with younger age in 703/081 (p<0.01). Of 160 IRRs, six (3.8%) were severe and 96% were mild/moderate. All IRRs were managed successfully without sequelae.

**Conclusion:** IRRs in the AMP studies were uncommon, typically mild or moderate, successfully managed at the research clinic and fully resolved. Laboratory analysis is ongoing to explore potential mechanisms of these reactions.

**Table 1.** Number of infusion reactions and participants with an infusion reaction by treatment group and clinical phenotype

| Phenotype in HVTN 704/HPTN 085 | No. of Infusion Reactions (%) <sup>a</sup> |                       |                            |                            |
|--------------------------------|--|-----------------------|----------------------------|----------------------------|
|                                | Overall<br>N=2699                          | Control<br>N=903      | VRC01<br>10 mg/kg<br>N=899 | VRC01<br>30 mg/kg<br>N=897 |
| Overall                        | 49<br>47 (1.7)                             | 16 (32.7)<br>15 (1.7) | 14 (28.6)<br>14 (1.6)      | 19 (38.8)<br>18 (2.0)      |
| Urticaria                      | 26<br>25 (0.9)                             | 2 (7.7)<br>2 (0.2)    | 10 (38.5)<br>10 (1.1)      | 14 (53.8)<br>13 (1.4)      |
| Dyspnea with rash              | 3<br>3 (0.1)                               | 2 (66.7)<br>2 (0.2)   | 0 (0.0)<br>0 (0.0)         | 1 (33.3)<br>1 (0.1)        |
| Dyspnea without rash           | 4<br>4 (0.1)                               | 1 (25.0)<br>1 (0.1)   | 1 (25.0)<br>1 (0.1)        | 2 (50.0)<br>2 (0.2)        |
| Other                          | 16<br>15 (0.6)                             | 11 (68.8)<br>10 (1.1) | 3 (18.8)<br>3 (0.3)        | 2 (12.5)<br>2 (0.2)        |
| Phenotype in HVTN 703/HPTN 081 | Overall<br>N=1924                          | Control<br>N=637      | VRC01<br>10 mg/kg<br>N=642 | VRC01<br>30 mg/kg<br>N=645 |
| Overall                        | 111<br>93 (4.8)                            | 12 (10.8)<br>11 (1.7) | 52 (46.8)<br>41 (6.4)      | 47 (42.3)<br>41 (6.4)      |
| Urticaria                      | 41<br>41 (2.1)                             | 2 (4.9)<br>2 (0.3)    | 17 (41.5)<br>17 (2.6)      | 22 (53.7)<br>22 (3.4)      |
| Dyspnea with rash              | 1<br>1 (0.1)                               | 0 (0.0)<br>0 (0.0)    | 1 (100.0)<br>1 (0.2)       | 0 (0.0)<br>0 (0.0)         |
| Dyspnea without rash           | 20<br>19 (1.0)                             | 2 (10.0)<br>2 (0.3)   | 14 (70.0)<br>13 (2.0)      | 4 (20.0)<br>4 (0.6)        |
| Other                          | 49<br>41 (2.1)                             | 8 (16.3)<br>7 (1.1)   | 20 (40.8)<br>17 (2.6)      | 21 (42.9)<br>17 (2.6)      |

<sup>a</sup>The denominator for percentages is the total number of infusion reactions within each phenotype.  
<sup>b</sup>Participants are counted once within each phenotype. The denominator for percentages is the number of enrolled participants (N).

## 719 INJECTION NETWORKS AND HIV PREVENTION SERVICES AMONG PEOPLE WHO INJECT DRUGS IN INDIA

**Neia Prata Menezes**<sup>1</sup>, Allison M. McFall<sup>1</sup>, Aylur K. Srikrishnan<sup>2</sup>, Canjeevaram K. Vasudevan<sup>2</sup>, Anand Santhanam<sup>2</sup>, Sunil S. Solomon<sup>2</sup>, David C. Celentano<sup>1</sup>, Gregory M. Lucas<sup>3</sup>, Shruti H. Mehta<sup>1</sup>

<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>YR Gaitonde Center for AIDS Research and Education, Chennai, India, <sup>3</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** Injection networks of people who inject drugs (PWID) may influence risk behaviors and HIV acquisition. In India, where HIV incidence is rising among PWID, HIV prevention strategies are available, but uptake is poor. We evaluate associations between injection network characteristics and recent engagement in HIV testing in the prior 6 months, medication for opioid use disorder (MOUD) and syringe service utilization in the prior month.

**Methods:** We recruited 11,745 PWID across 12 Indian cities using respondent-driven sampling in 2016–17. Eligible participants who were ≥18 years old and reported injection drug use in the past 2 years, underwent HIV testing and completed surveys assessing network characteristics, substance use, and HIV prevention program utilization. Among HIV-negative PWID reporting injection in the prior 6 months, we used multilevel logistic regression models, weighted by site-level PWID population size, to evaluate relationships between injection network size and self-reported engagement in each service separately (HIV testing, MOUD, syringe services). Models were adjusted for age, gender, injection frequency, substance use, recent incarceration, and engagement in the other services.

**Results:** 7,380 PWID (63%) were HIV-negative and reported recent injection drug use (median age: 28; 98% male). Recent engagement in HIV prevention services was poor: 12% received an HIV test, 19% engaged in MOUD and 22% in syringe services; 3% engaged in all 3 services. Median injection network size was 3 [IQR: 1–5]; 17% reported injecting with >10 PWID; only 0.9% reported sharing injection equipment with a known HIV-positive PWID in the prior 30 days. Injection network size was not associated with recent HIV testing. Those reporting sharing injection equipment with a known HIV-positive PWID were more likely to report a recent HIV test (adjusted OR [AOR]=2.54; p=0.04). Injecting with >10 vs. 0–1 PWID in the prior 30 days was associated with decreased MOUD use (AOR=0.55; p<0.01) but increased syringe service use (AOR=1.54; p<0.01).

**Conclusion:** In this large community-based sample across India, injection network size was differentially associated with use of HIV prevention services. These associations may reflect perceived need or access as MOUD and HIV testing tend to be facility based whereas syringe services are commonly community-based. Community-based delivery of HIV testing and MOUD may help overcome barriers.

**Table 1.** Association between injection drug network characteristics and recent engagement in HIV prevention services among HIV-negative people who inject drugs (PWID) reporting active injection drug use in prior 6 months across 12 cities in India, 2016–17 (n=7,380)<sup>a</sup>

|   | HIV testing in the prior 6 months |         | MOUD use in the prior month |         | Syringe service program utilization in the prior month |         |
|---|-----------------------------------|---------|-----------------------------|---------|--|---------|
|   | AOR                               | p-value | AOR                         | p-value | AOR  | p-value |
| <b>No. of PWID injected with in prior 30 days</b>                                     |                                   |         |                             |         |  |         |
| 0–1   | ref                               |         | ref                         |         | ref  |         |
| 2–10  | 0.75                              | 0.15    | 0.62                        | <0.01** | 1.34   | <0.01** |
| >10   | 0.76                              | 0.33    | 0.55                        | <0.01** | 1.53   | <0.01** |
| <b>Shared injection equipment with HIV-positive PWID in prior 30 days<sup>b</sup></b> |                                   |         |                             |         |  |         |
| No  | ref                               |         | ref                         |         | ref  |         |
| Yes   | 2.55                              | 0.04**  | 0.63                        | 0.07    | 2.46   | 0.08    |

<sup>a</sup>All models weighted by estimated site-level PWID population size and adjusted for age, gender, region, household income, marital status, education, intervention site, frequency of injection, alcohol use, heroin vs. buprenorphine use, and utilization of two other HIV prevention services.

<sup>b</sup>Among those reporting sharing needle or syringe injection equipment with PWID network member in prior 30 days.

\*\* Statistically significant at  $\alpha = 0.05$  significance level.

MOUD=medication for opioid use disorder, AOR=adjusted odds ratio

## 720 PREVALENCE & DETERMINANTS OF EARLY SEX RESUMPTION POSTCIRCUMCISION (RAKAI, UGANDA)

**Alex Daama**<sup>1</sup>, Dorean Nabukalu<sup>1</sup>, Edward N. Kankaka<sup>1</sup>, Doreen Tuhebe<sup>2</sup>, Absalom Ssettuba<sup>1</sup>, Fred Nalugoda<sup>1</sup>, Tom Lutalo<sup>1</sup>, Joseph Kagaayi<sup>1</sup>, Gertrude F. Nakigozi<sup>1</sup>, Michelle Adler<sup>1</sup>, Lisa Mills<sup>3</sup>, Ronald Gray<sup>4</sup>, Maria Wawer<sup>1</sup>, Godfrey Kigozi<sup>1</sup>

<sup>1</sup>Rakai Health Sciences Program, Kalisizo, Uganda, <sup>2</sup>Makerere University, Kampala, Uganda, <sup>3</sup>Centers for Disease Control and Prevention, Kampala, Uganda, <sup>4</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Voluntary medical male circumcision (VMMC) reduces HIV infection in men by 50%–60%. The Uganda Ministry of Health (MoH) guidelines recommend abstaining from sexual activity for at least 42 days after VMMC to promote complete wound healing. Early resumption of sexual intercourse post VMMC increases risk of HIV infection among HIV-negative men and possibly increases risk of male to female transmission. However, previous reports show almost half (48%) of men in Uganda resume sexual activity early following VMMC with higher rates of early sexual resumption (ESR) among married men, men with multiple partners, and men diagnosed as HIV-positive. In view of this, we estimated changes in prevalence and assessed risk factors of ESR among VMMC men in Rakai, Uganda, over an eight-year period.

**Methods:** We analyzed data from male participants aged 15–49 years in the Rakai Community Cohort Study who self-reported having received VMMC in one of the four successive survey rounds conducted between June 2013 and October 2020 (–). We estimated ESR prevalence at each round, and to understand risk factors associated with ESR, we used modified Poisson regression to estimate adjusted prevalence ratios (aPR). Statistical significance was tested at 5% level of significance

**Results:** Of the 1,832 circumcised men included in the study, 485 (26.5%) reported ESR. ESR significantly decreased over the study period, from 45.1% reported in Round 1 (June 2013 – January 2015); to 21.8% in Round 2 (February 2015 – August 2016); 21.1% in Round 3 (September 2016 – May 2018); and 16.9% in Round 4 (June 2018 – October 2020) (p-trend<0.001). Across the three survey rounds (R1, R2 & R3), ESR prevalence was consistently higher among currently married men than men who were never married (aPR, 1.8; p=0.001). In R3, ESR prevalence was higher among men who reported more than one sexual partner than men with one partner (aPR, 1.6; p=0.004). Education and age were inconsistently associated with ESR across all four survey rounds. Overall, men who reported primary school as their highest level of education reported ESR more often than those with post-primary education (aPR, 2.6; p=0.008). Residence and known HIV status were not associated with ESR across all survey rounds.

**Conclusion:** Overall, ESR post-VMMC declined from June 2013 to October 2020; and was generally more common among men who are married, had multiple sex partners, and lower levels of education. More strategic interventions are needed to reduce ESR among these men.

Table 04: Multivariate model showing trends in determinants of ESR

| Factor                           | SURVEY ROUND 16<br>Adjusted PR | SURVEY ROUND 17<br>Adjusted PR | SURVEY ROUND 18<br>Adjusted PR | SURVEY ROUND 19<br>Adjusted PR                        |
|----------------------------------|--------------------------------|--------------------------------|--------------------------------|---|
| <b>Education level</b>           |                                |                                |                                |   |
| Post-primary                     | 1                              | 1                              | 1                              | 1   |
| Primary                          | 1.23[0.97,1.56]                | 1.17 [0.80,1.71]               | 1.12[0.75,1.68]                | 2.40[1.29,5.35]**                                     |
| None                             | 1.25[0.80,1.94]                | 0.53[0.08,3.61]                | 1.53 [0.85,2.75]               | 2.40[0.35,16.30]<br>1.32[0.49,3.55]                   |
| <b>Apprenticeship</b>            |                                |                                |                                |   |
| Age group                        |                                |                                |                                |   |
| 15-19                            | 1                              | 1                              | 1                              | 1   |
| 20-24                            | 1.22 [0.74,2.00]               | 1.36[0.65,2.86]                | 1.19[0.50,2.83]                | 1.58[0.64,3.88]                                       |
| 25-34                            | 1.16 [0.70,1.94]               | 1.37[0.63,2.97]                | 1.79[0.70,4.54]                | 1.72[0.64,4.60]                                       |
| 35-44                            | 1.55[0.92,2.63]                | 1.38[0.60,3.16]                | 1.39[0.53,3.64]                | 2.19[0.77,6.23]                                       |
| 45+                              | 1.16[0.59,2.25]                | 0.95[0.29,3.11]                | 0.99[0.29,3.39]                | 7.35e-07[1.94e-07,2.79e-06]<br>***                    |
| <b>Residence</b>                 |                                |                                |                                |   |
| Trading centre                   | 1                              | 1                              | 1                              | 1   |
| Agrarian                         | 1.05 [0.77,1.44]               | 1.25[0.80,1.95]                | 1.16[0.69,1.95]                | 0.79[0.38,1.63]                                       |
| Fishing                          | 1.20[0.86,1.67]                | 0.94[0.56,1.58]                | 1.30[0.77,2.18]                | 0.68[0.29,1.64]                                       |
| <b>Number of sexual partners</b> |                                |                                |                                |   |
| One partner                      | 1                              | 1                              | 1                              | 1   |
| More than one partner            | 1.17 [0.95,1.45]               | 1.26[0.90,1.76]                | 1.59[1.16,2.20]**              | 1.20[0.68,2.11]<br>8.57e-07[3.55e-07,2.07e-06]<br>*** |
| None                             | 1.19 [0.83,1.70]               | ***                            | 0.47[0.07,3.25]                | ***   |
| <b>HIV status</b>                |                                |                                |                                |   |
| Negative                         | 1                              | 1                              | 1                              | 1   |
| Positive                         | 0.77[0.57,1.05]                | 1.24[0.80,1.92]                | 1.08 [0.78,1.50]               | 0.56[0.22,1.43]                                       |
| <b>Marital status</b>            |                                |                                |                                |   |
| Never married                    | 1                              | 1                              | 1                              | 1   |
| Currently married                | 1.83[1.30,2.57]**              | 2.46[1.50,4.06]***             | 2.22[1.22,4.03]**              | 1.30[0.61,2.76]                                       |
| Not married                      | 1.29[0.82,2.01]                | 1.34[0.59,3.04]                | 1.96[0.99,3.90]*               | 0.82[0.30,2.23]                                       |

\*p<0.05, \*\* p<0.01, \*\*\* p<0.001

**721 RISK FOR REPEAT STI EPISODES AMONG KENYAN ADOLESCENT GIRLS AND YOUNG WOMEN**

Melody Wang<sup>1</sup>, Kenneth Tapia<sup>1</sup>, Lynda M. Oluoch<sup>1</sup>, Murugi Micheni<sup>1</sup>, Stacy Selke<sup>1</sup>, Catherine Kiptinness<sup>1</sup>, Bhavna Chohan<sup>1</sup>, Anna Wald<sup>1</sup>, Kenneth Nguni<sup>1</sup>, Nelly R. Mugo<sup>1</sup>, Alison C. Roxby<sup>1</sup>

<sup>1</sup>University of Washington, Seattle, WA, USA

**Background:** Adolescent girls and young women (AGYW) are disproportionately affected by HIV and STIs. Understanding behavioral and biological risk factors for incident STI, especially for sexually inexperienced girls, can help determine prevention strategies.

**Methods:** AGYW aged 16-20 in Thika, Kenya, were followed prospectively over 5 years. AGYW entered the cohort if HIV and HSV-2 seronegative and reporting no or only one prior sexual partner. Quarterly visits assessed N. gonorrhoea (GC), C. trachomatis (CT), and T. vaginalis (TV) by nucleic acid testing, HSV-2 and HIV by ELISA, and bacterial vaginosis (BV) by Gram stain. Self-reported sexual activity was recorded by questionnaire and further validated using Y-chromosome PCR tests, spermatozoa on Gram stain, pregnancy, or STI test results, and amended if incongruent. Generalized Estimating Equation (GEE) models were used to determine relative risk of correlates of STIs over time.

**Results:** Among 400 participants, 299 sexually active AGYW were included in analyses. Two girls acquired HIV and were excluded. At least one STI (CT, GC, HSV-2, TV) was detected in 56% (168/299) of AGYW. Subsequently, 40% of those AGYW (67/168) later experienced two or more STI events. CT infections were most common, observed in 85% of AGYW with single STI events (n=101) and in 72% of AGYW with multiple STI events (n=67). AGYW had a median of 7 visits (IQR:4-9) and at least one STI event was present at 21% of visits post-sexual initiation. AGYW with BV at the same visit had a significantly increased risk of any STI (CT/GC/TV/HSV-2) (RR: 1.49; 95%CI: 1.09–2.03; P=0.01), as did AGYW reporting a new sexual partner in the last 3 months (RR: 2.02; 95%CI: 1.26–3.26; P<0.01). AGYW with evidence of sexual activity who did not disclose that they were sexually active had almost 3-fold increased risk of STI events (RR: 2.72; 95%CI: 1.93–3.83; P<0.001) compared to those who disclosed sexual initiation. AGYW with >1 STI had similar risk factors as those with one STI, suggesting behaviors were not different. Condom use was low and not correlated with risk of STIs (RR: 0.97; 95%CI: 0.61-1.56; P=0.91).

**Conclusion:** Over the critical years near sexual debut, AGYW demonstrated high incidence of multiple STIs. Over time, AGYW with new sexual partners, and those who did not disclose sexual activity were at highest risk for subsequent STI events. Interventions to prevent STIs are needed for AGYW with limited sexual experience and for those not able to disclose sexual activity.

Table 1. GEE model of relative risk for STI events (CT/GC/TV/HSV-2) over 5 years.

|  | Relative Risk | Robust SE | P-value | 95% Confidence Interval |
|--|---------------|-----------|---------|-------------------------|
| Age at study visit   | 0.97          | 0.044     | 0.543   | 0.89-1.06               |
| Longer time between menarche and sexual initiation               | 0.94          | 0.034     | 0.115   | 0.88-1.01               |
| Bacterial Vaginosis (BV) (Nugent Score>7) present at study visit | 1.49          | 0.235     | 0.012** | 1.09-2.03               |
| Number of new sexual partners reported in past 3 months          | 2.02          | 0.492     | 0.004** | 1.26-3.26               |
| Sex not self-reported but evident from other measures            | 2.72          | 0.477     | 0.000** | 1.93-3.83               |
| Condom used in past 3 months                                     | 0.97          | 0.234     | 0.906   | 0.61-1.56               |

**722 BACTERIAL VAGINOSIS TRENDS AMONG ADOLESCENTS BEFORE AND AFTER SEXUAL ACTIVITY**

Alison C. Roxby<sup>1</sup>, Bhavna Chohan<sup>2</sup>, Kenneth Tapia<sup>1</sup>, Stacy Selke<sup>1</sup>, Melody Wang<sup>1</sup>, Catherine Kiptinness<sup>2</sup>, Lynda M. Oluoch<sup>2</sup>, Kenneth Nguni<sup>3</sup>, Anna Wald<sup>1</sup>, Nelly R. Mugo<sup>2</sup>

<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Kenya Medical Research Institute, Nairobi, Kenya, <sup>3</sup>Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

**Background:** Bacterial vaginosis (BV) is a risk factor for HIV and sexually transmitted infections and adverse reproductive outcomes in adolescent girls and young women (AGYW). It is unknown when BV develops among AGYW at the time of sexual debut.

**Methods:** Kenyan AGYW ages 16-20 with no or limited self-reported sexual activity were enrolled in a cohort and followed quarterly for BV swabs and STI testing. BV was diagnosed by Nugent score from vaginal Gram stain. Trends in BV were described over time; relative risk of correlates of BV were estimated using generalized estimating equations. Models were adjusted for age, sexual activity, income, rural/urban home, STIs, and time from menarche.

**Results:** Of 400 AGYW enrolled, 322 (80.5%) reported no prior sexual activity at enrollment. At first visit, 21 of 389 girls (5.6%) had prevalent BV. Over median follow-up of 48 months (inter-quartile range (IQR) 24-57), AGYW had a median of 11 BV tests (IQR=5-15); 166 (43%) had at least 1 BV diagnosis. Prior to reported sex, 2.8% of visits had BV, compared to 13.7% of visits post sexual activity. BV was 3.5x more likely after sexual debut (95%CI 2.3-5.3, p<0.001). AGYW reporting more frequent/recent sex (>1 act in prior 3 months) had higher risk of BV (RR 1.80 compared to those reporting ≤1 act, CI 1.36-2.39; p<0.01). In an adjusted model, sexual initiation remained the most significant risk for BV (aRR 2.23, CI 1.3– 3.9; p<0.01). Other covariates associated with increasing risk of BV included recent sexual activity, urban home, and having no income. STI diagnosis at the same visit was strongly associated with BV, with chlamydia aRR 1.78 (CI 1.4-2.3; p<0.01), gonorrhoea aRR 1.77 (CI 1.1-3.0, p=0.03). HSV-2 coinfection was also associated with BV, aRR 1.8 (CI 1.3-2.5, p<0.01). BV protective factors included self-reported virginity (RR 0.40, CI 0.21-0.75, p<0.01) and longer time between menarche and first sex: AGYW with 5 years, aRR 1.5, (CI 1.04-2.16, p=0.03).

**Conclusion:** Using detailed longitudinal observation of AGYW from pre-sexual activity to older age, this work establishes that Kenyan adolescents have almost no BV prior to sexual debut. Initiation of sexual activity was the strongest risk factor for BV, and increased number of sexual acts was highly linked to BV diagnosis. Given the health consequences of BV, our finding of protective factors, including less BV among those with longer duration between menarche and sex, should be explored.

| Risk of bacterial vaginosis among Kenyan adolescent girls and young women. (Adjusted GEE model) |                     |                         |         |
|---|---------------------|-------------------------|---------|
| Characteristic  | Relative Risk (aRR) | 95% Confidence Interval | P-value |
| Age at visit, years   | 1.00                | (0.92, 1.07)            | 0.9     |
| Penile-vaginal sexual intercourse   | 2.23                | (1.28, 3.88)            | 0.005   |
| Penile-vaginal sexual activity in last 3 months   |                     |                         |         |
| Yes   | 1.38                | (1.04, 1.83)            | 0.024   |
| Reported never penile-vaginal intercourse   | 0.40                | (0.21, 0.75)            | 0.004   |
| Income in the last 3 months, Ksh  |                     |                         |         |
| >1,000 Ksh (>\$10 USD)  | Ref.                | -                       | -       |
| 1-1,000 (\$1-10 USD)  | 1.23                | (0.79, 1.91)            | 0.3     |
| None  | 1.74                | (1.25, 2.41)            | 0.001   |
| Lives in urban area   | 1.37                | (1.07, 1.75)            | 0.013   |
| Time between menarche and first penile-vaginal sexual intercourse                               |                     |                         |         |
| >5 years  | Ref.                | -                       | -       |
| 3-5 years   | 1.13                | (0.81, 1.59)            | 0.5     |
| ≤3 years  | 1.50                | (1.04, 2.16)            | 0.029   |
| Not available   | 1.31                | (0.89, 1.92)            | 0.171   |
| Chlamydia at same visit as BV   | 1.78                | (1.37, 2.30)            | <0.001  |
| Gonorrhea at same visit as BV   | 1.77                | (1.04, 2.99)            | 0.034   |
| Herpes simplex virus 2 antibody positive  | 1.83                | (1.33, 2.50)            | <0.001  |

| Characteristic   | Univariable Mixed Effects Model OR (95% CI) | P      | Multivariable Mixed Effects Model aOR (95% CI) | P      |
|--|---|--------|--|--------|
| Primary care patient (Ref: Not a primary care patient)   | 0.97 (0.02 to 52.9)                         | 0.99   | 0.30 (0.05 to 1.84)                            | 0.19   |
| Age at qualifying STI encounter  | 1.50 (0.59 to 3.81)                         | 0.39   | 0.90 (0.61 to 1.33)                            | 0.61   |
| Assigned male sex at birth (Ref: Assigned female sex at birth)   | 22.3 (0.15 to 3348)                         | 0.23   | 40.2 (3.32 to 487)                             | 0.004  |
| Qualifying STI diagnosis after FDA approval for adolescent PrEP Use (Ref: STI Diagnosis before FDA Approval) | 6.72 (0.34 to 131)                          | 0.21   | 1.60 (0.10 to 25.8)                            | 0.74   |
| Time elapsed from diagnosis to FDA approval for adolescent PrEP use (per month) (Ref: Time 0 = May 16, 2018) | 1.10 (0.83 to 1.44)                         | 0.52   | 1.02 (0.67 to 1.56)                            | 0.92   |
| Repeat qualifying STI encounter (Ref: Index Visit)   | 6.09 (0.64 to 57.5)                         | 0.12   | 3.41 (0.89 to 13.1)                            | 0.07   |
| Adolescent medicine specialist (Ref: Not Adolescent Medicine)  | 28.4 (0.26 to 3132)                         | 0.16   | 1.64 (0.39 to 7.02)                            | 0.50   |
| Diagnosed with chlamydia (Ref: No Chlamydia diagnosis)   | 5.0 (0.31 to 80.6)                          | 0.26   | 0.49 (0.13 to 1.90)                            | 0.31   |
| Diagnosed with gonorrhea (Ref: No gonorrhea diagnosis)   | 0.07 (0 to 11.18)                           | 0.31   | 0.08 (0.01 to 1.02)                            | 0.05   |
| Diagnosed with syphilis (Ref: No syphilis diagnosis)   | 2.16 (0 to 40065)                           | 0.88   | 4.94 (0.43 to 56.8)                            | 0.20   |
| Diagnosed with rectal STI (Ref: No rectal diagnosis)   | 521 (44.5 to 6106)                          | <0.001 | 61.7 (6.63 to 574)                             | <0.001 |

## 723 HIV PrEP COUNSELING AMONG BLACK YOUTH DIAGNOSED WITH BACTERIAL STI, 2014-2019

Dovie L. Watson<sup>1</sup>, Pamela A. Shaw<sup>1</sup>, Danielle T. Petsis<sup>2</sup>, Julia Pickel<sup>2</sup>, José A. Bauermeister<sup>1</sup>, Ian Frank<sup>1</sup>, Sarah M. Wood<sup>2</sup>, Robert Gross<sup>1</sup>

<sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA

**Background:** Youth account for a disproportionate number of new HIV infections and bacterial STI infections; however, pre-exposure prophylaxis (PrEP) use among youth is limited. We evaluated rates of PrEP counseling among non-Hispanic Black youth after bacterial STI diagnosis.

**Methods:** We conducted a retrospective cohort study of non-Hispanic Black youth who received care at two academically affiliated clinics in Philadelphia, PA between June 2014 and June 2019. All met CDC PrEP eligibility criteria due to qualifying bacterial STI in the past 6 months based on sex assigned at birth and sex of sexual partners. Using episode-level multivariable mixed effects logistic regression analyses, we compared PrEP counseling rates for youth who received primary care services versus those who did not (521 qualifying STI episodes among 416 PrEP-eligible youth).

**Results:** Among this cohort of 416 PrEP-eligible youth, 35 (8%) received PrEP counseling within 6 months of qualifying STI diagnosis. As shown in Table 1, receipt of primary care services was not significantly associated with receipt of PrEP counseling after adjusting for patient- and health care-level factors (aOR 0.30 (95% CI 0.05 to 1.84)). Being assigned male sex at birth (aOR = 40.2, 95% CI 3.32 to 487) and having a rectal STI (aOR = 61.7, 95% CI 6.63 to 574) were strongly associated with receipt of PrEP counseling. Fourteen patients started emtricitabine (FTC) / tenofovir disoproxil fumarate (TDF) PrEP; 12 of whom were sexual gender minority (SGM) patients assigned male sex at birth who received primary care services. We found an 11% (5) HIV seroconversion rate among SGM assigned male sex at birth and an overall rate of 1% among the cohort—none were diagnosed with HIV at index qualifying STI encounter.

**Conclusion:** These findings demonstrate that PrEP-eligible non-Hispanic Black youth receive PrEP counseling at low rates. Patients assigned female sex at birth were disproportionately and significantly less likely to receive PrEP counseling than patients assigned male sex at birth. Although our findings clearly indicate that PrEP counseling occurred primarily among SGM patients assigned male sex at birth, our effect estimates were unstably large due to the rare occurrence of the outcome among non-SGM patients. These findings support the need for robust investment in PrEP-inclusive sexual health services that are widely implemented and culturally tailored to non-Hispanic Black youth at risk of HIV acquisition, particularly cisgender heterosexual females.

## 724 HIV AND SYPHILIS IN THE DISTRICT OF COLUMBIA

Kaitlin Liroff<sup>1</sup>, Seble Kassaye<sup>1</sup>, Amanda B. Spence<sup>1</sup>, Princy N. Kumar<sup>1</sup>, Madhuri Natarajan<sup>1</sup>, Rachel Harold<sup>2</sup>, Kerri Dorsey<sup>2</sup>, Rupali K. Doshi<sup>2</sup>, Adam J. Visconti<sup>2</sup>

<sup>1</sup>Georgetown University, Washington, DC, USA, <sup>2</sup>District of Columbia Department of Health, Washington, DC, USA

**Background:** HIV and syphilis co-infection comprised 39% of primary or secondary (early) syphilis cases in the District of Columbia (DC) in 2018. These stages of syphilis are associated with increased HIV transmissibility. People living with HIV (PLH) are also at risk for severe manifestations of syphilis. We sought to determine effectiveness of syphilis treatment by assessing time from diagnosis to treatment, variables that influence time to treatment, and adequacy of therapy to identify opportunities to reduce ongoing transmission.

**Methods:** The DC Department of Health created a limited data set of all individuals with syphilis between January 1, 2015 and December 31, 2019. Additional variables included: age, sex, ward, stage of syphilis, diagnosis date, HIV status, CD4+ T cell count, HIV viral load (VL), reporting and treating facility, and treatment type and duration. Adequacy of treatment was delineated by the Centers for Disease Control 2015 syphilis treatment guidelines. Data was analyzed using logistic regression to identify factors associated with delayed treatment >14 days from diagnosis.

**Results:** Among 2,723 individuals, 8% (219/2723) were female, 90.3% (2459/2723) were male, average age was 36.9 years (range: 0–93), and 44.7% (1216/2723) were co-infected with HIV. Among 921 PLH with VL data, 39.2% (363/921) had undetectable VL and 26.5% (145/921) had VL >1,000 copies/mL. Among 893 PLH, 59% (581/893) had a CD4 >500. Overall treatment adequacy for treatment of early syphilis was 99.9%. Factors associated with delay of treatment included detectable HIV VL (between 20 and 199 copies/mL OR=1.630; p=0.0380; and VL >10,000 copies/mL OR=1.825; p=0.0387). Other variables associated with delay in treatment are listed in table 1.

**Conclusion:** Although our dataset demonstrates almost perfect treatment for early syphilis, we identified that nearly a third of PLH co-infected with syphilis have VL > 1000 copies/mL. Unsuppressed VL compounded with significant delays in treatment in this subgroup highlights the importance of targeting public health efforts to engage this population in care. This is necessary for successful treatment of both syphilis and HIV with the goal of reducing transmission of both pathogens and to decrease the long-term sequelae associated with both untreated diseases.

Table 1. Factors associated delayed treatment greater than 14 days from time of diagnosis

| Effect   | Odds Ratio | 95% CI          | p-value |
|--|------------|-----------------|---------|
| HIV VL   | 1.630      | (1.027, 2.585)  | 0.0380  |
| 20 and 199 vs. HIV VL < 20 > 10,000 vs. HIV VL < 20            | 1.825      | (1.032, 3.227)  | 0.0387  |
| Black vs. White  | 1.824      | (1.010, 3.295)  | 0.0464  |
| Refused/unknown vs. White                                      | 2.111      | (1.088, 4.097)  | 0.0272  |
| Transgender vs. Female   | 5.118      | (0.834, 31.395) | 0.0777  |
| Early Latent Syphilis vs. Primary and Secondary Syphilis       | 3.204      | (1.959, 5.239)  | <0.0001 |
| Reporting Provider Type: Private practice vs. FQHC or CHC      | 0.081      | (0.010, 0.690)  | 0.0215  |
| Treatment Provider Type: Hospital-based clinic vs. FQHC or CHC | 0.160      | (0.024, 1.055)  | 0.0568  |

HIV= Human Immunodeficiency Syndrome; VL=Viral Load; FQHC= Federally Qualified Health Center; CHC= Community Health Center

\*adjusted for age, HIV VL, CD4 categorical, race/ethnicity, gender, ward, stage of syphilis diagnosis, concurrent CT/GC, reporting provider type, treatment provider type

725 WITHDRAWN

726 DISPARITIES IN FAMILY PLANNING AMONG WOMEN LIVING WITH HIV IN THE SOUTHEASTERN US

Manasa R. Bhatta<sup>1</sup>, Aihua Bian<sup>1</sup>, Jamison Norwood<sup>1</sup>, Bryan Shepherd<sup>1</sup>, Jeffrey Nelson<sup>1</sup>, Imani Ransby<sup>1</sup>, Megan Turner<sup>1</sup>, Timothy Sterling<sup>1</sup>, Jessica L. Castilho<sup>1</sup>  
<sup>1</sup>Vanderbilt University, Nashville, TN, USA

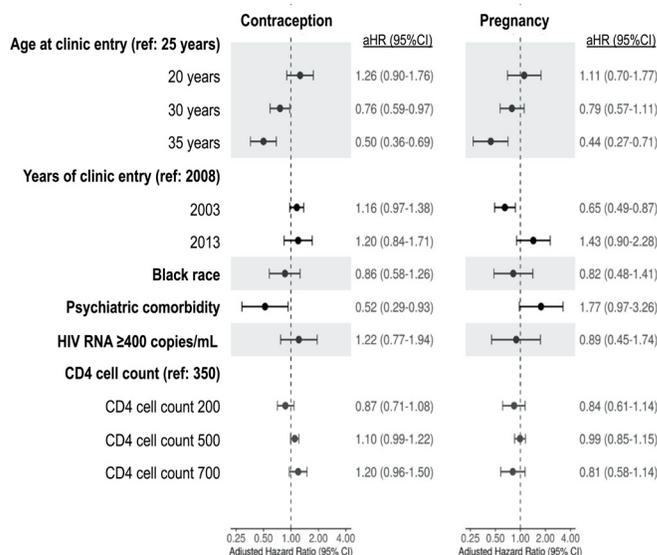
**Background:** Compared to women without HIV, women living with HIV (WLH) are more likely to use less effective contraception. Unanticipated effects of antiretroviral therapy (ART) on pregnancy outcomes have highlighted the need for effective family planning. Contraception use among WLH in the United States over time has not been well described.

**Methods:** This observational cohort study examined factors associated with contraception initiation among cis-gender women aged 18-45 years in longitudinal care at Vanderbilt's HIV clinic from 1998-2018. Women with hysterectomies or bilateral tubal ligations (BTL) prior to entry were excluded. Contraception included oral, transdermal, vaginal ring, and injectable hormonal contraception; intrauterine devices; hormonal implants; and BTL. Annual prevalence estimates of contraception use, weighted for person-time, described use over time. Cox proportional hazard models compared factors associated with incident contraception use and pregnancy, including age, year of clinic entry, race, psychiatric comorbidity, smoking, substance use, and time-varying CD4 cell count, HIV RNA, and ART use. Restricted cubic splines were used for continuous covariates.

**Results:** At clinic entry, median age was 31 years (IQR 25-37), median CD4 cell count was 392 cells/μL (IQR 182-444), and 76 (13%) of the 737 women had undetectable HIV viral load. Women were followed for a median of 4.1 years (IQR 1.3-8.1). Only 46 (6%) women were on contraception and 164 (22%) were pregnant at clinic entry. Of the remaining 527 women, 116 (16%) initiated contraception and 61 (9%) became pregnant during follow-up. The median prevalence of any contraception use among non-pregnant women was 31% (IQR 31-32%) and was stable throughout the study period. While not associated with contraception use (p=0.10), recent year of clinic entry increased risk of pregnancy (p=0.01) in adjusted models (Figure). Younger age increased risk of pregnancy and contraception use (both p<0.001). Psychiatric comorbidity decreased hazard of contraception and tended to increase hazard of pregnancy. Race, substance use, CD4 cell count, HIV RNA, smoking, and ART use were not associated with contraception nor pregnancy.

**Conclusion:** Most WLH did not use any contraception at baseline nor during follow-up. Pregnancy risk increased with recent clinic entry, whereas contraception initiation remained stable. More effective contraception counseling is needed among WLH, particularly younger women and those with psychiatric comorbidities.

Factors associated with incident contraception use and pregnancy during follow-up



727 THE PREVALENCE AND CLUSTERING OF MENOPAUSAL SYMPTOMS IN WOMEN LIVING WITH HIV

Hajra Okhai<sup>1</sup>, Caroline Sabin<sup>1</sup>, Katharina Haag<sup>1</sup>, Lorraine Sherr<sup>1</sup>, Rageshri Dhairyawan<sup>2</sup>, Richard Gilson<sup>1</sup>, Burns Fiona<sup>1</sup>, Shema Tariq<sup>1</sup>

<sup>1</sup>University College London, London, UK, <sup>2</sup>Barts Health NHS Trust, London, UK

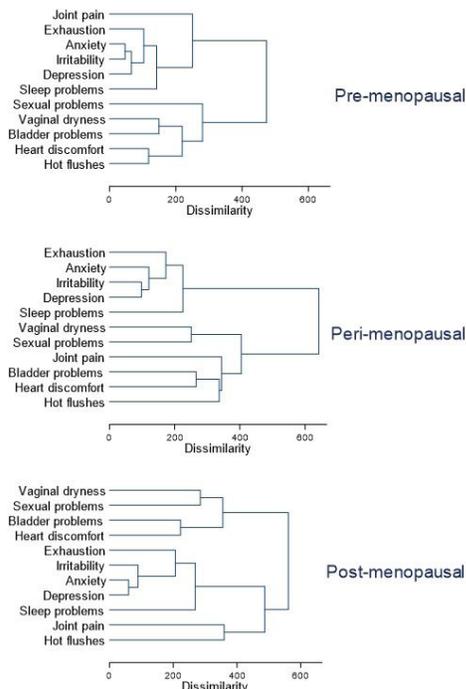
**Background:** An increasing proportion of women living with HIV (WLWH) are now experiencing the menopause. We describe the clustering of menopausal symptoms in a large, representative sample of WLWH in England to understand the burden and inform care pathways.

**Methods:** We included 709 women aged 45-60 from PRIME, an observational study of WLWH. The Menopause Rating Scale was used to capture the severity of each of 11 menopausal symptoms (0: None/little to 4: Very severe). Hierarchical agglomerative cluster analysis was used to describe the clustering of symptoms by menopausal status (pre-, peri- and post-).

**Results:** Median age was 49 years (interquartile range: 47-52). The majority were Black African (71.7%), had completed at least secondary education (89.4%), were currently employed (68.9%) and in a relationship (57.1%). Overall, 211 (29.8%), 117 (16.5%), 182 (25.7%) and 199 (28.1%) women reported no/little, mild, moderate or severe symptoms/complaints, respectively. Joint pain (66.4%) was the most commonly reported symptom, followed by hot flushes (63.0%), exhaustion (61.6%) and sleep problems (61.4%). All symptoms were more common among peri- and post-menopausal women. Amongst pre-menopausal women, joint pain, exhaustion, anxiety, irritability, depression and sleep problems clustered together (Figure). The remaining symptoms (sexual problems, vaginal dryness, bladder problems, heart discomfort and hot flushes) formed a second cluster. Amongst peri-menopausal women, joint pain clustered more closely with bladder problems, heart discomfort and hot flushes, and there was apparent clustering between vaginal dryness and sexual problems in this group. Among post-menopausal women, the cluster of anxiety, exhaustion, irritability and depression seen in peri-menopausal women remained, with bladder problems and heart discomfort now clustering with vaginal dryness and sexual problems, and joint pain and hot flushes forming a third cluster.

**Conclusion:** In the first study to explore the clustering of menopausal symptoms among WLWH, we report a high proportion of menopausal symptoms. Whilst exhaustion, anxiety, depression, irritability and sleep problems remained closely related across all menopausal stages, urogenital and somatic symptom clusters become more distinct in the peri- and post-menopause. These data allow a nuanced understanding of symptoms and potential aetiologies in women aging with HIV, facilitating the most appropriate and effective support.

Figure: Dendrogram representing the clustering of menopausal symptoms reported by women in PRIME at each menopausal status



## 728 LONG-ACTING COFORMULATED BIODEGRADABLE IMPLANT FOR HIV PREVENTION AND CONTRACEPTION

Linying Li<sup>1</sup>, Archana Krovi<sup>1</sup>, Chasity Norton<sup>1</sup>, Pafio Johnson<sup>1</sup>, Guadalupe Jimenez<sup>1</sup>, Christine Areson<sup>1</sup>, Ariane Van der Straten<sup>2</sup>, Leah Johnson<sup>1</sup>

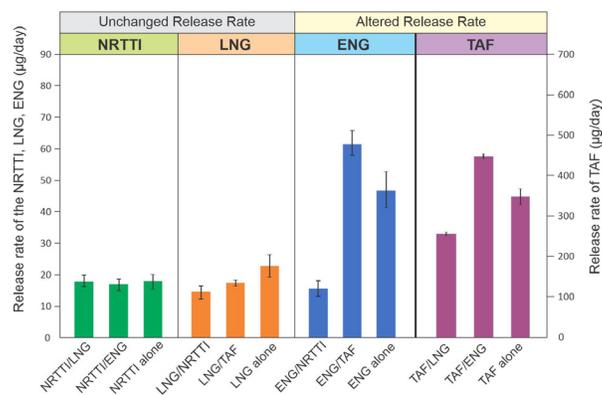
<sup>1</sup>RTI International, Research Triangle Park, NC, USA, <sup>2</sup>RTI International, Berkeley, CA, USA

**Background:** Women worldwide face multiple health risks such as unintended pregnancy and HIV. Multipurpose prevention technologies (MPTs) can simultaneously address the need for contraception and prevention of infectious disease with one product. Here, we are developing a long-acting (LA) biodegradable implant comprising a multi-drug formulation for HIV prevention and contraception.

**Methods:** We selected two well-characterized progestins, levonorgestrel (LNG) and etonogestrel (ENG), and two inhibitors of the reverse transcriptase, the NRTI tenofovir alafenamide (TAF) and an investigational NRTTI. Polycaprolactone extruded tubes were filled with various ARV-hormone combinations and heat sealed. In-vitro release from devices (in phosphate buffered saline, pH 7.4 at 37°C) was monitored using UV-vis spectroscopy or high-performance liquid chromatography (HPLC), while maintaining sink conditions.

**Results:** We evaluated 20 MPT multi-drug formulations, each containing varying ratios of an ARV, a hormone, and an excipient (e.g., 50/35/15, 50/25/25 wt.%). Implants comprising the multi-drug formulations exhibit linear release of both ARV and hormone up to 12-months. Variations in the drug to excipient ratios did not affect the release rate, indicating a membrane-controlled release process. Interestingly, the release rates of TAF and ENG are affected by the presence of another drug within the formulations, whereas the release rates of the NRTTI and LNG remained comparable to their respective single-drug formulations (Figure 1). Specifically, co-formulating the NRTTI with ENG lowered the release of ENG while maintaining the release rate of the NRTTI. On the contrary, co-formulation of ENG and TAF exhibited enhanced release rates for both drugs.

**Conclusion:** We developed a LA MPT implant containing multi-drug formulations for sustained delivery of ARV and hormones with zero-order kinetics. Co-formulating ARVs and hormones showed varied effect in vitro on the release rate of each drug, increasing our ability to tailor the release rates of ARVs and hormones via the co-formulation process. Using a single co-formulated implant can simplify administration and willingness to use and may improve compliance by eliminating the need for insertion of multiple rods containing individual drugs.



## 729 ENSURING HIV SERVICE CONTINUITY DURING THE COVID-19 PANDEMIC IN KAMPALA, UGANDA

Esther M. Nasuuna<sup>1</sup>, Muganzi Alex<sup>1</sup>, Grace Namayanja<sup>2</sup>, Nakade Shamim<sup>1</sup>, Kavuma Paul<sup>1</sup>, Rhoda M. Mwondha<sup>1</sup>, Donna Kabatesi<sup>2</sup>, Nelson Kalema<sup>1</sup>, Kigozi Joanita<sup>3</sup>

<sup>1</sup>Infectious Disease Institute, Kampala, Uganda, <sup>2</sup>Centers for Disease Control and Prevention, Kampala, Uganda, <sup>3</sup>Infectious Diseases Institute, Kampala, Uganda

**Background:** In March 2020, the World Health Organization declared COVID-19 a pandemic. On March 21, the Ugandan government instituted a nationwide lockdown, suspending public transport and closing schools and businesses. This threatened to interrupt antiretroviral therapy (ART) service delivery to people living with HIV (PLHIV) in urban areas and those who had traveled away from home. We describe how the Infectious Diseases Institute (IDI) ensured continued HIV service delivery in Kampala, Uganda.

**Methods:** IDI serves 215,427 PLHIV receiving ART in Kampala and Wakiso districts. From April to June 2020, IDI scaled up multi-month ART refills and contacted PLHIV by phone to tailor ART refill delivery options to ensure uninterrupted access. Options included home or specified community point delivery in which expert clients using motorcycles made deliveries (a modality adopted by the ministry of health in Uganda); referrals to health facilities within walking distance of clients' lock down locations; drug pickup by a designee; and, for PLHIV receiving third-line ART, refill delivery via the national laboratory sample transport system. IDI also launched the Kampala Capital City Authority COVID-19 hotline and CDC-supported toll-free line so that PLHIV could seek guidance on how to access treatment. To avoid service interruptions due to reduced public transportation for staff, IDI provided transport for selected health workers to and from the health facility.

**Results:** During the lockdown, of the 191,576 PLHIV with scheduled visits, 105,037 (55%) missed their appointment and required immediate follow-up. A total of 205,296 PLHIV received an ART refill. Through IDI's efforts, 194,873 (those who had missed appointments and unscheduled walk-ins) were reached. Most (177,433 [86%]) were served at their routine facility, 17,440 (8%) received refills in the community, and 10,423 (5%) received refills at facilities outside the region. Only 51,589 (26%) received 3- or 6-month refills.

**Conclusion:** With innovations and program modification, IDI ensured continuity of ART services in an urban population during the lockdown. Scale-up of multi-month refills may be needed during the COVID-19 pandemic and future emergencies to ensure uninterrupted ART services for PLHIV. Tailored refill options for HIV service delivery can improve retention.

## 730 IMPACT OF COVID-19 ON HIV PREVENTION AND CARE INDICATORS IN SAN FRANCISCO, CA

Hyman Scott<sup>1</sup>, Elise S. Mara<sup>1</sup>, Sharon Pipkin<sup>1</sup>, Jen Hecht<sup>2</sup>, Jason Bena<sup>2</sup>, Janessa Broussard<sup>2</sup>, Diane V. Havlir<sup>3</sup>, Susan P. Buchbinder<sup>1</sup>, Ling Hsu<sup>1</sup>

<sup>1</sup>San Francisco Department of Public Health, San Francisco, CA, USA, <sup>2</sup>San Francisco AIDS Foundation, San Francisco, CA, USA, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA

**Background:** The COVID-19 pandemic has resulted in disruptions to HIV prevention and care services access throughout the US. We sought to evaluate the impact of service disruption from the COVID-19 pandemic response on key Getting to Zero San Francisco (GTZSF) HIV prevention and care metrics of HIV antibody (Ab) and HIV viral load (VL) testing, Pre-exposure prophylaxis (PrEP) use, and the continuum of HIV care.

**Methods:** Reports of positive and negative HIV Ab testing from 4 laboratories and a large community testing site (CTS), and HIV VL testing for people living with HIV reported to the San Francisco Department of Public Health were included. We compared the number of HIV Ab and VL tests, and PrEP visits at the CTS each month from January-October 2020 with the corresponding months in 2019. The continuum of HIV care was calculated for new HIV diagnoses in January-June 2020 compared to the same period in 2019.

**Results:** From January-October 2020, the mean number of monthly laboratory-based HIV Ab tests decreased from 4,400/month in 2019 to 3,644/month in 2020 (Table); and from 1,382/month to 766/month at the CTS. April 2020 had the lowest number of HIV tests, a reduction of 54% in laboratory reporting and 88% in the CTS compared with April 2019; there was a partial rebound through October 2020. While the number of positive HIV tests was lower per month in 2020 compared with 2019, the proportion HIV positive remained stable throughout the study period (2020: Range 0.9-1.4%; 2019: Range 1.1-1.6%). HIV VL testing also declined in 2020 similar to the trend of HIV testing with the largest decline (57%) in April 2020. Overall, PrEP visits at the CTS declined more than 31% in the study period; the largest decline (90%) occurred in April 2020 with partial rebound through October 2020. From January to June 2020, 75 new HIV diagnoses were identified, compared with 101 in 2019. Linkage to care within 1 month was 93% in 2020 and 97% in 2019; HIV viral suppression within 6 months was 75% in 2020 and 76% in 2019.

**Conclusion:** We have observed substantial reductions in HIV Ab and VL testing during the COVID-19 pandemic, and likely decreased HIV case finding. PrEP care engagement also declined dramatically; however rapid linkage to care and viral suppression after HIV diagnosis remained robust. Continued monitoring of key HIV prevention and care metrics is essential to assessing the complex impact of COVID-19 on the GTZSF goals, and developing tailored mitigation responses.

Table: Year-over-year changes in the number of laboratory-based HIV antibody and viral load tests, and PrEP visits at a large community testing site (CTS) in San Francisco.

| Month     | HIV antibody tests |      |          | HIV viral load tests |      |          | PrEP visits at CTS |      |          |
|-----------|--------------------|------|----------|----------------------|------|----------|--------------------|------|----------|
|           | 2019               | 2020 | % Change | 2019                 | 2020 | % Change | 2019               | 2020 | % Change |
| January   | 4544               | 4765 | 5%       | 2627                 | 2430 | -7%      | 684                | 736  | 8%       |
| February  | 4121               | 4423 | 7%       | 2109                 | 2039 | -3%      | 568                | 693  | 22%      |
| March     | 4488               | 3308 | -26%     | 2214                 | 1607 | -27%     | 729                | 394  | -46%     |
| April     | 4561               | 2087 | -54%     | 2419                 | 1034 | -57%     | 642                | 65   | -90%     |
| May       | 4561               | 2792 | -39%     | 2296                 | 1609 | -30%     | 715                | 231  | -68%     |
| June      | 4110               | 3689 | -10%     | 2216                 | 2262 | 2%       | 690                | 393  | -43%     |
| July      | 4471               | 3878 | -13%     | 2257                 | 1895 | -16%     | 683                | 599  | -12%     |
| August    | 4308               | 3746 | -13%     | 2186                 | 1762 | -19%     | 698                | 536  | -23%     |
| September | 4190               | 3809 | -9%      | 2165                 | 2062 | -5%      | 644                | 481  | -25%     |
| October   | 4643               | 3945 | -15%     | 2513                 | 2015 | -20%     | 729                | 460  | -37%     |

**731 IMPACT OF COVID-19 ON PrEP PRESCRIPTIONS IN THE UNITED STATES: A TIME SERIES ANALYSIS**

Ya-Lin A. Huang<sup>1</sup>, Weiming Zhu<sup>1</sup>, Athena Kourtis<sup>1</sup>, Irene Hall<sup>1</sup>, Karen W. Hoover<sup>1</sup>  
<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:**

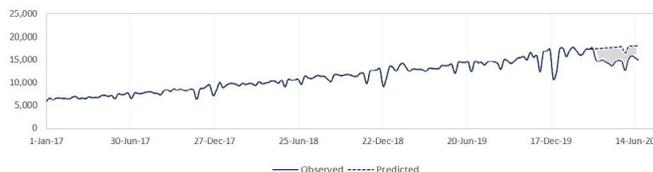
On March 13, 2020 a national emergency was declared and protective measures were implemented in response to the COVID-19 pandemic. PrEP prescriptions had increased in the United States since 2014, but shutdown because of COVID-19 resulted in decreased use of health services. The objective of this study was to evaluate the impact of the COVID-19 on PrEP prescriptions in the United States.

**Methods:** We analyzed data from the IQVIA Real World Data-Longitudinal Prescriptions Database from 2017 to the end of June 2020. Using a validated algorithm, we identified PrEP prescriptions and new PrEP users. We used a Bayesian structural time series model to predict the trajectory in PrEP prescriptions for the period of March 15-June 27, 2020 in the absence of the pandemic. The prediction was computed based on the pre-COVID-19 weekly PrEP data from January 1, 2017 to March 14, 2020 in the IQVIA database and adjusted for decreased PrEP prescriptions during holidays. The impact of COVID-19 was inferred by the differences between predicted and observed time series. We stratified the effect of COVID-19 on PrEP prescriptions by age group, insurance type, and among 10 states with most PrEP prescriptions prior to the national emergency declaration.

**Results:** In the absence of the pandemic, our time series model predicted that there would have been 264,281 PrEP prescriptions during March 15-June 27, 2020 and we observed 222,589 PrEP prescriptions in the IQVIA database, a 15.8% reduction after the emergency declaration (Figure). The model predicted

43,636 new PrEP users during the same time period and we observed 29,971 new PrEP users, a 31.3% reduction after the emergency declaration. The impact of the pandemic on PrEP prescriptions was greater for those who paid for PrEP with cash (34.3% reduction in PrEP prescriptions; 44.3% reduction in new PrEP users). The COVID-19 impact varied among the 10 states with the most PrEP prescriptions prior to the pandemic, ranging from 6.8% to 25.1% reductions in PrEP prescriptions and 19.8% to 48.1% reductions in new PrEP users. The number of new PrEP users began to increase towards the end of June 2020. **Conclusion:** Closures during the initial phase of the COVID-19 pandemic resulted in decreases in PrEP prescriptions and even more in new PrEP users. Ongoing monitoring is warranted to assess whether the impact has abated since June 2020. The reasons for decreased PrEP prescriptions could be lack of access to care or decreased risk behavior during the pandemic.

Figure. Trend in weekly number of observed and predicted PrEP prescriptions from January 1, 2017 to June 27, 2020



**732 IMPACT OF COVID-19 AMONG PEOPLE LIVING WITH HIV IN THE AFRICAN COHORT STUDY (AFRICOS)**

Nicole Dear<sup>1</sup>, Allahna Esber<sup>1</sup>, Ajay Parikh<sup>1</sup>, Emma Duff<sup>1</sup>, Michael Iroezindu<sup>1</sup>, Emmanuel Bahemana<sup>1</sup>, Hannah Kibuuka<sup>2</sup>, John Owuoth<sup>1</sup>, Jonah Maswai<sup>1</sup>, Trevor A. Crowell<sup>1</sup>, Christina Polyak<sup>1</sup>, Julie Ake<sup>1</sup>

<sup>1</sup>U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA, <sup>2</sup>Makerere University-Walter Reed Project, Kampala, Uganda

**Background:** The COVID-19 pandemic and national responses to mitigate this public health threat have disrupted activities of daily living with economic and health impacts globally. The extent of these disruptions is evolving. Our objectives were to characterize participants who missed study visits during the pandemic and assess the impact of COVID-19 on HIV outcomes, employment, food security and trauma among people living with HIV (PLWH).

**Methods:** AFRICOS began enrolling adults at risk for HIV and PLWH at 12 PEPFAR-supported clinics in Tanzania, Uganda, Kenya, and Nigeria in 2013. At 6-monthly visits sociodemographic questionnaires were administered and clinical outcomes assessed. Chi-squared tests were used to describe differences between those presenting for and missing a study visit since the pandemic began, using data from participants' most recent visit before 19 March 2020. Generalized estimating equations were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) comparing social and clinical indicators before and during the pandemic. Models were adjusted for age, sex and site; food security models were also adjusted for employment status. Analyses were restricted to those with a pre-COVID-19 visit on or after 1 January 2019 and at least one visit during the pandemic.

**Results:** As of 1 November 2020, 1023 (44.5%) of 2298 PLWH with a pre-COVID-19 visit since 1 January 2019 had a visit during the pandemic. PLWH who missed a study visit during COVID-19 were less adherent to antiretroviral therapy (ART) (70.0% vs 88.6%, p<0.001), less adherent to clinic visits (77.5% vs 95.4%, p<0.001) and a greater proportion had a viral load ≥1000 copies/mL on ART (17.5% vs 4.6%, p<0.001). Participants seen during the pandemic were less likely to be food secure (aOR: 0.57, 95% CI: 0.44 - 0.74) and more likely to have cut/reduced one or more meals per day (aOR: 1.75, 95% CI: 1.36 - 2.25; table). No significant impacts of COVID-19 were observed on clinic visit or ART adherence, employment, or Post-Traumatic Stress Disorder. Among 665 PLWH with available data, 597 (89.8%) had a ≥3-month supply of ART during COVID-19.

**Conclusion:** PLWH missing study visits during COVID-19 were less engaged in care prior to the pandemic. Innovations such as multi-month dispensing, telemedicine, and other differentiated service delivery strategies should be used to retain PLWH in care. During the pandemic, HIV outcomes remained stable, but food insecurity needs to be addressed.

Table. Impact of the COVID-19 pandemic on indicators of HIV care, employment, food security and trauma among PLWH

|  | OR (95% CI)               | aOR (95% CI)              |
|--|---------------------------|---------------------------|
| Missed Clinic Visits <sup>a</sup>                  | 1.25 (0.85 – 1.85)        | 1.26 (0.84 – 1.88)        |
| ART Adherence <sup>b</sup>                         | 0.98 (0.79 - 1.22)        | 0.99 (0.78 - 1.25)        |
| Employed   | 0.97 (0.90 - 1.04)        | 0.87 (0.73 - 1.03)        |
| Food Security <sup>c</sup>                         | <b>0.56 (0.43 - 0.71)</b> | <b>0.57 (0.44 - 0.74)</b> |
| Meals Reduced <sup>d</sup>                         | <b>1.75 (1.37 – 2.23)</b> | <b>1.75 (1.36 – 2.25)</b> |
| Post-Traumatic Stress Disorder (PTSD) <sup>e</sup> | 0.90 (0.59 - 1.37)        | 0.90 (0.58 - 1.40)        |

<sup>a</sup> Missed clinic visits: defined as one or more missed clinic visits in the past 6 months

<sup>b</sup> ART adherence: defined as one or more missed doses of ART in the past 30 days

<sup>c</sup> Food security: defined as having enough food to eat in the past 12 months

<sup>d</sup> Meals reduced: defined as one or more meals cut or reduced in size per day on average because there was not enough food or money for food

<sup>e</sup> PTSD indicated by a PTSD score  $\geq 3$

Bold indicates significance at  $p < 0.05$

### 733 POTENTIAL IMPACT OF COVID-19-RELATED DISRUPTIONS ON HIV IN YAOUNDÉ, CAMEROON

Romain Silhol<sup>1</sup>, Kate M. Mitchell<sup>1</sup>, Sharmistha Mishra<sup>2</sup>, Lily Geidelberg<sup>1</sup>, Anna Bowring<sup>3</sup>, Christinah Mukandavire<sup>4</sup>, Sheree Schwartz<sup>5</sup>, Dobromir Dimitrov<sup>6</sup>, Mathieu Maheu-Giroux<sup>7</sup>, Iliassou Mfochive Njindam<sup>5</sup>, Serge C. Billong<sup>8</sup>, Daniel Levitt<sup>9</sup>, Peter Vickerman<sup>10</sup>, Stefan Baral<sup>5</sup>, Marie-Claude Boily<sup>1</sup>

<sup>1</sup>Imperial College London, London, UK, <sup>2</sup>University of Toronto, Toronto, Canada, <sup>3</sup>Burnet Institute, Melbourne, Australia, <sup>4</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>5</sup>Johns Hopkins School of Public Health, Baltimore, MD, USA, <sup>6</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>7</sup>McGill University, Montreal, Canada, <sup>8</sup>University of Yaoundé, Yaoundé, Cameroon, <sup>9</sup>CARE USA, New York, NY, USA, <sup>10</sup>University of Bristol, Bristol, UK

**Background:** In Yaoundé, Cameroon, coverage of HIV prevention and treatment services has increased with an estimated 50% of people living with HIV accessing antiretroviral treatment (ART) in 2018. The HIV burden remains high among key populations, despite increases in condom use and ART among men who have sex with men (MSM), female sex workers (FSW) and their clients. The COVID-19 pandemic may temporarily alter sexual behaviours and disrupt HIV services, including ART initiation and condom distribution (with reduced outreach). We explored the potential effects of these changes on the HIV epidemic among key populations in Yaoundé.

**Methods:** We used a deterministic mathematical model of HIV transmission calibrated to local demographic, behavioural, and HIV epidemiology data. We estimated the relative difference in cumulative new HIV infections and HIV-related deaths from 04/2020 to 03/2021 (median, 95% uncertainty interval), under scenarios assuming individual temporary 6-month reductions in HIV prevention/treatment services or changes in sexual risk behaviour in all or some risk groups compared to a base-case scenario assuming no COVID-19-related disruptions.

**Results:** A 6-month cessation of ART initiation alongside a 50% reduction of viral suppression among ART-users for 6-month could increase annual HIV infections by 21% (18-25%) and HIV-related deaths by 9% (7-10%): half of these impacts are attributable to ART discontinuations among key populations. A 50% reduction in condom use across all partnerships would lead to 23% (15-31%) more infections overall and 36% (20-55%) more infections among key populations (Figure). Reducing condom use among key populations (initially >80% for FSW, ~65% for MSM) to the levels of use among lower-risk populations (~30%), would result in 14% (9-23%) more infections overall, and 20% (8-36%), 44% (26-97%), and 29% (15-56%) more infections among MSM, FSW and their clients, respectively. A 75% reduction in paid sex due to closure of sex work-associated venues would have little effect on reducing infections overall: 4% (1-8%) if currently high condom-use and ART levels among FSW are maintained.

**Conclusion:** Temporary disruptions in condom use and ART services, especially among key populations, may have a substantial impact on HIV in Yaoundé. Ensuring access to condoms among FSW and MSM despite reduced outreach during the COVID-19 pandemic should be a priority to minimise its potential impact.

### HIV testing and ART

Relative reduction in viral suppression of 50%

No new ART initiations

### Condom use

All condom use decreases by 50%

Non-commercial condom use decreases by 50%

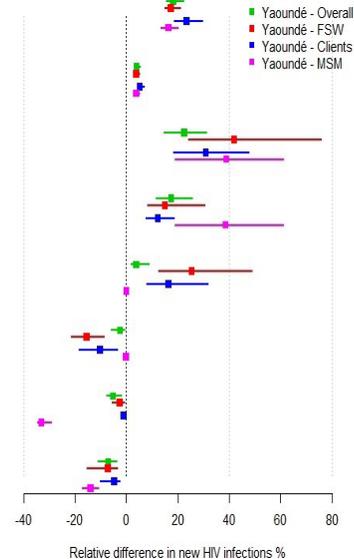
Commercial condom use decreases by 50%

### Sexual behaviours

Number of commercial partners reduced by 50%

Number of male partners of MSM reduced by 50%

Number of casual partners reduced by 50%



### 734 VISIT COMPLETION DURING THE TELEMEDICINE TRANSITION IN EARLY MONTHS OF THE PANDEMIC

Walid El-Nahal<sup>1</sup>, Nikki Shen<sup>2</sup>, Catherine Lesko<sup>2</sup>, Jeanne C. Keruly<sup>1</sup>, Kelly Gebo<sup>1</sup>, Bryan Lau<sup>2</sup>, Anthony T. Fojo<sup>1</sup>, Richard Moore<sup>1</sup>, Geetanjali Chander<sup>1</sup>

<sup>1</sup>Johns Hopkins School of Medicine, Baltimore, MD, USA, <sup>2</sup>Johns Hopkins School of Public Health, Baltimore, MD, USA

**Background:** Prior to the COVID-19 pandemic, evidence on telemedicine use in people with HIV was limited. In response to the pandemic, telemedicine use was widely adopted. On March 16th, 2020, the John G. Bartlett Specialty Practice converted from exclusively in-person visits to mostly telemedicine visits. We studied the impact of this transition on visit completion.

**Methods:** We conducted separate analyses of patients in the Johns Hopkins HIV Clinical Cohort scheduled for visits in the 14 weeks before and in the 14 weeks after the transition. For each 14-week period, we calculated the percentage of people who completed at least one visit. We calculated odds ratios (OR) for having completed  $\geq 1$  visit, associated with demographic and clinical factors in each period.

**Results:** Pre-transition and post-transition characteristics of the study sample were: 1,580 vs 1,598 patients, 61% vs. 63% male, 80% vs. 78% black, 56 vs. 57 median age, 92% vs. 92% viral suppression, and 25% vs. 24% people with a history of injection drug use (IDU) by chart review. Pre-transition, 79% of patients completed  $\geq 1$  visit. Post-transition, 1,315 patients (82%) were scheduled for telemedicine visits and 283 were scheduled for in-person visits. Visit completion in the post-transition period was 84%, overall. Visit completion for telemedicine visits was 98%. Telemedicine visits were conducted 70% by phone, 30% by video. A History of IDU was associated with lower odds of visit completion, pre-transition OR=0.84 [95% confidence interval (CI):0.64,1.11], post-transition OR=0.74 [CI:0.55,0.99]. Substance use in recent years was associated with lower odds of visit completion post-transition: heroin use OR=0.39 [CI:0.24,0.62] and cocaine use OR=0.57 [CI:0.37,0.86]. OR for visit completion associated with tobacco use pre-transition was 0.64 [CI:0.50,0.82] and post-transition was 0.86 [CI:0.66,1.14]. Age 60+ was associated with higher odds of visit completion pre-transition (OR=1.67 [CI:1.16,2.41]) but not post-transition (OR=0.87 [CI:0.57,1.35]).

**Conclusion:** Moving to telemedicine visits during the pandemic provided access to services, with a higher proportion of patients completing  $\geq 1$  visit, but many patients were only able to complete a telemedicine visit by phone. The impact of expanding access to telemedicine on probability of visit completion and possibly differential access by subsets of the population should be explored more once data for longer time periods are available, as should the long-term impact on other clinical outcomes.

Visit Completion Pre- and Post-Transition

|  | At Least 1 Scheduled Visit Pre-transition<br>Dec 2019 – Mar 15 2020 | At Least 1 Scheduled Visit Post-transition<br>Mar 16 – Jun 30 2020 |
|--|---|--|
| All People Scheduled                         | (n = 1,580)   | (n = 1,598)  |
| Completed ≥ 1 Visits                         | 1,245 (79%)   | 1,340 (84%)  |
| <b>Age Category</b>                          |   |  |
| 20-39  | Reference   | Reference  |
| 40-59  | 1.17 (0.84, 1.65)   | 0.80 (0.53, 1.22)  |
| 60+  | <b>1.67 (1.16, 2.41)</b>  | 0.87 (0.57, 1.35)  |
| <b>Male</b>                                  | 1.24 (0.97, 1.59)   | 0.99 (0.75, 1.30)  |
| <b>Race</b>                                  |   |  |
| White  | Reference   | Reference  |
| Black  | 0.94 (0.68, 1.31)   | 0.95 (0.66, 1.35)  |
| Other  | 1.15 (0.56, 2.36)   | 1.53 (0.65, 3.56)  |
| <b>Virally Suppressed</b>                    | 1.50 (0.99, 2.27)   | 1.30 (0.81, 2.09)  |
| <b>HIV Risk Factor</b>                       |   |  |
| Men who have Sex with Men                    | 1.39 (0.98, 1.97)   | 1.07 (0.73, 1.56)  |
| Heterosexual Intercourse                     | <b>0.75 (0.59, 0.96)</b>  | 0.87 (0.67, 1.15)  |
| History of Injection Drug Use                | 0.84 (0.64, 1.11)   | <b>0.74 (0.55, 0.99)</b>   |
| <b>Recent<sup>†</sup> Heroin Use</b>         | 0.73 (0.46, 1.20)   | <b>0.39 (0.24, 0.62)</b>   |
| <b>Recent<sup>†</sup> Cocaine Use</b>        | 0.91 (0.61, 1.37)   | <b>0.57 (0.37, 0.86)</b>   |
| <b>Recent<sup>†</sup> Hazardous ETOH Use</b> | 0.93 (0.64, 1.36)   | 0.89 (0.59, 1.35)  |
| <b>Recent<sup>†</sup> Smoking</b>            | <b>0.64 (0.50, 0.82)</b>  | 0.86 (0.66, 1.14)  |
| <b>History of Depression</b>                 | 0.81 (0.63, 1.03)   | 0.98 (0.75, 1.28)  |
| <b>Duration in Care</b>                      |   |  |
| < 1 year                                     | Reference   | Reference  |
| 1-5 years                                    | 0.88 (0.45, 1.75)   | 1.26 (0.62, 2.57)  |
| 6-10 years                                   | 0.80 (0.41, 1.57)   | 1.28 (0.63, 2.62)  |
| 10+ years                                    | 1.11 (0.59, 2.10)   | 1.38 (0.72, 2.65)  |
| <b>Patient Reported Outcomes</b>             | (n = 597)   | (n = 604)  |
| <b>Depressed Mood</b>                        | 1.14 (0.75, 1.73)   | 0.85 (0.55, 1.31)  |
| <b>Anxiety</b>                               | 1.08 (0.63, 1.84)   | 1.13 (0.74, 2.35)  |
| <b>Trauma Symptoms</b>                       | 1.24 (0.58, 2.63)   | 0.84 (0.40, 1.76)  |

<sup>†</sup> Recent is defined as identified on latest abstraction from the electronic medical record. 82% of latest abstractions were conducted from 2018 onward.

**735 MODELLING THE IMPACT OF COVID-19-RELATED DISRUPTIONS ON HIV IN THE UNITED STATES**

**Kate M. Mitchell<sup>1</sup>**, Dobromir Dimitrov<sup>2</sup>, Romain Silhol<sup>1</sup>, Lily Geidelberg<sup>1</sup>, Mia Moore<sup>2</sup>, Albert Liu<sup>3</sup>, Chris Beyrer<sup>4</sup>, Kenneth H. Mayer<sup>5</sup>, Stefan Baral<sup>6</sup>, Marie-Claude Boily<sup>1</sup>

<sup>1</sup>Imperial College London, London, UK, <sup>2</sup>Fred Hutchinson Cancer Research Center, Seattle, WA, USA, <sup>3</sup>San Francisco Department of Public Health, San Francisco, CA, USA, <sup>4</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>5</sup>Harvard TH Chan School of Public Health, Boston, MA, USA

**Background:** During the COVID-19 pandemic, gay, bisexual and other men who have sex with men (MSM) in the United States (US) have reported similar or fewer sexual partners and reduced access to HIV testing and care. Pre-exposure prophylaxis (PrEP) use has declined. We estimated the potential impact of COVID-19 on HIV incidence and HIV-related mortality among US MSM.

**Methods:** We used a calibrated HIV transmission model for MSM in Baltimore, Maryland, and available data on COVID-19-related disruptions (from national online surveys of US MSM and from a Boston clinic with extensive PrEP experience) to predict impacts of data-driven reductions in sexual partners (0% or 25% - based on different surveys), condom use (5%), HIV testing (20%), viral suppression (VS; 10%), PrEP initiations (72%), PrEP use (9%) and ART initiations (50%), exploring different disruption durations. We estimated the median (95% credible interval) relative change in cumulative new HIV infections and HIV-related deaths among MSM over 1 and 5 years from the start of COVID-19-related disruptions, compared with a scenario without COVID-19-related disruptions.

**Results:** A 6-month 25% reduction in sexual partners among Baltimore MSM, without HIV service changes, could reduce new HIV infections by 12.2%(11.7,12.8%) and 3.0%(2.6,3.4%) over 1 and 5 years, respectively. In the absence of changes in sexual behaviour, the 6-month data-driven disruptions to condom use, testing, VS, PrEP initiations, PrEP use and ART initiations combined were predicted to increase new HIV infections by 10.5%(5.8,16.5%) over 1 year, and by 3.5%(2.1,5.4%) over 5 years. A 25% reduction in partnerships offsets the negative impact of these combined service disruptions on new HIV infections (overall reduction 3.9%(-1.0,7.4%) and 0.0%(-1.4,0.9%) over 1 and 5 years, respectively), but not on HIV-related deaths (corresponding increases 11.0%(6.2,17.7%), 2.6%(1.5,4.3%).) Of the different service disruptions, a 6-month 10% reduction in VS was predicted to have the greatest impact, increasing new infections by 6.4%(2.6,11.9%) and HIV-related deaths by 9.5%(5.2,15.9%) over 1 year, without changes in sexual behaviour. The predicted impacts of reductions in partnerships or VS doubled if they lasted 12 months or if disruptions were twice as large.

**Conclusion:** Maintaining access to ART and adherence support is of the utmost importance to minimise excess HIV-related mortality due to COVID-19 restrictions in the US, even if accompanied by reductions in sexual partnerships.

**736 THE IMPACT OF COVID-19 RESTRICTIONS ON HIV SERVICES AMONG KEY POPULATIONS IN NIGERIA**

**Moses Katbi<sup>1</sup>**, Adefisayo Adedoyin<sup>2</sup>, Helina Meri<sup>1</sup>, Kent Klindera<sup>3</sup>, Adeoye Adegboye<sup>1</sup>, Abdulmalik Abubakar<sup>1</sup>, Amalachukwu Ukaere<sup>2</sup>, Abdulsamad Salihu<sup>2</sup>, Wole Fajemisin<sup>2</sup>, Segun K. Fatoye<sup>2</sup>, Rachel Goldstein<sup>1</sup>

<sup>1</sup>United States Agency for International Development, Abuja, Nigeria, <sup>2</sup>Society for Family Health, Abuja, Nigeria, <sup>3</sup>United States Agency for International Development, Washington, DC, USA

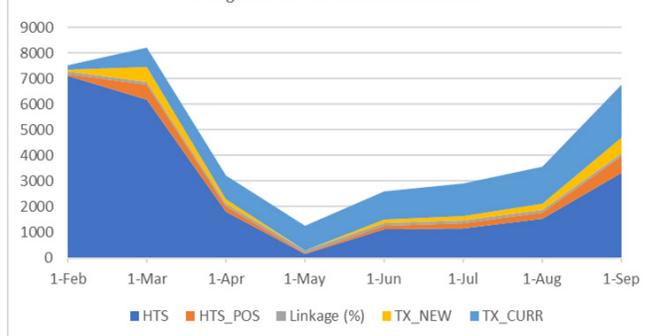
**Background:** Nigeria recorded the first case of COVID 19 in February 2020 and imposed non pharmaceutical interventions including full-scale lockdown from April-May 2020. The lockdown and ensuing restrictions had an impact on routine HIV/AIDS services delivery among key population individuals (e.g. men who have sex with men, people who inject drugs, sex workers, transgender individuals and people in prisons). This study analyzed the impact of COVID-19 lockdown and restrictions on HIV/AIDS services including testing, identification of positives and linkage to treatment on a PEPFAR program in North Eastern Nigeria.

**Methods:** A multi-centric retrospective study conducted in two states to assess the impact of COVID 19 on access to HIV services (testing, positives identified and linkage to HIV treatment). HIV services data from November 2019 to September 2020 was collected from source documents. We classified this period into four: pre-COVID (September 2019-March 2020), COVID lockdown (April-May 2020), COVID restrictions (June-July 2020) and relaxed restrictions (August-September 2020). A simple trend analysis of HIV services was done using a combination chart. Linear regression was conducted to understand the impact of COVID-19 on HIV services. The model for the Linear regression curve was plotted to compare the observed values with predicted (Linear) values.

**Results:** We observed a sharp dip in HIV services during COVID lockdown and restriction (figure 1). The plots indicated a linear relationship between the month services were provided and HIV service outcome. The months services were conducted significantly predicted the number of testing (F(1,9) = 20.689, p = .001), positives (F(1,9) = 15.857, p=0.003) and treatment (F(1,9) = 16.699, p=0.003) provided, accounting for 66.3%, 59.8% and 61.1% of the variation in number of HIV tests conducted, total HIV positive clients identified and clients placed on treatment respectively with adjusted R2 = 0.663, 0.598, and 0.611 for testing, positive and treatment respectively. The linear curve estimation showed that the actual HIV services outcome were below the projected estimated target in the months most affected by COVID 19 lockdown and restrictions.

**Conclusion:** New pandemics can have negative effects on the control of other diseases such as HIV where health gains have been achieved in the past. Hence, a robust pandemic readiness plan must be developed for a possible second wave of COVID-19 to sustain the gains from several years of HIV intervention efforts.

Fig. 1 trend analysis of HIV services outcome showing dip in results during COVID lockdown and restrictions



**737 COVID-19 PANDEMIC IMPACT ON ACCESS TO HIV SERVICES FOR KEY POPULATIONS IN INDIA**

**Allison M. McFall<sup>1</sup>**, Shruti H. Mehta<sup>1</sup>, Jon Kawatachi<sup>1</sup>, Sunil S. Solomon<sup>2</sup>, Aylur K. Srikrishnan<sup>3</sup>, David C. Celentano<sup>1</sup>, Gregory M. Lucas<sup>2</sup>

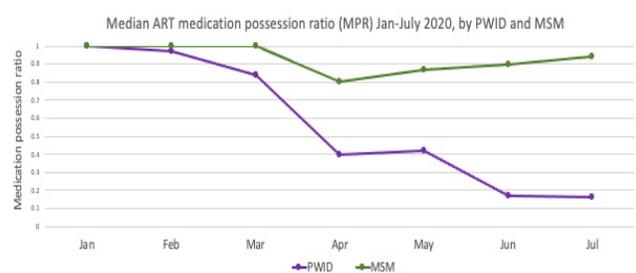
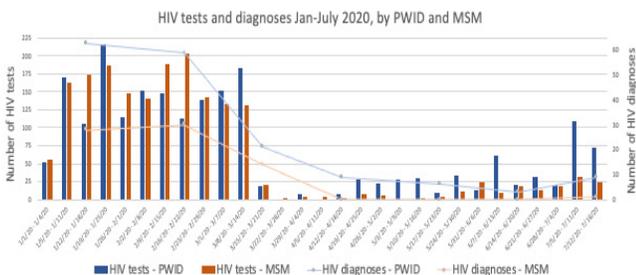
<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>YR Gaitonde Center for AIDS Research and Education, Chennai, India

**Background:** The COVID-19 pandemic and associated lockdowns threaten to diminish gains made with respect to HIV epidemic control. The impacts are likely to be most profound among marginalized key populations in resource-limited settings.

**Methods:** Beginning in 2013, we initiated integrated care centers (ICCs) targeting PWID and MSM; ICCs are currently active in 16 Indian cities (8 PWID, 8 MSM) providing core and population-focused HIV services, including HIV counseling/testing, STI testing, and linkage to/monitoring of ART from government facilities. To understand the pandemic's impact on service access, we compared service utilization among ICC clients early in the pandemic (March-July 2020) to pre-pandemic (Jan-Feb 2020) levels. Specifically, we assessed: 1) numbers of clients accessing HIV testing and STI screening as well as new HIV diagnoses, and 2) for HIV-infected clients on ART in December 2019, the medication possession ratio (MPR). The MPR is the percentage of days in a month that a client had an available dose of ART based on the client's government ART book.

**Results:** Overall, 14,415 clients visited an ICC from Jan-July 2020. Compared to pre-pandemic levels, the total number of clients receiving services at the ICC began declining in March and dropped to ~25% normal capacity in May and only returned to ~35% capacity by July. HIV testing declined by 88% beginning in mid-March (PWID 90%, MSM 84%) followed by a modest increase in April/May, but levels did not return to pre-pandemic levels (Figure panel A); a similar pattern was seen for STI testing. HIV diagnoses had a sharp decline in March/April with no significant rebound to pre-pandemic levels by July; among MSM there was only one new diagnosis in all of April-July, compared to ~30 each month in January and February. Compared to February, the median MPR in April declined by nearly 60% for PWID (from an MPR of 97% to 40%) and by 20% for MSM (100% to 80%). The MPR continued to fall for PWID reaching a nadir of 16% in July; by contrast the MPR climbed back to near pre-pandemic levels for MSM by July (Figure panel B).

**Conclusion:** The COVID-19 pandemic has led to significant decreases in use of HIV-related services among key populations in India. PWID have fared substantially worse than MSM in both preventive and treatment services. This presents an opportunity for increased transmission and incidence among groups that are already disproportionately impacted by the HIV epidemic.



**738 HIV TREATMENT/RETENTION IN SUB-SAHARAN AFRICA BEFORE AND DURING THE COVID-19 PANDEMIC**

**Danielle Fernandez<sup>1</sup>**, Catherine Godfrey<sup>2</sup>, Sherri L. Pals<sup>1</sup>, Ikwo Oboho<sup>1</sup>, George K. Siberry<sup>3</sup>, Hammad Ali<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>Office of the Global AIDS Coordinator, Washington, DC, USA, <sup>3</sup>United States Agency for International Development, Washington, DC, USA

**Background:** In sub-Saharan Africa (SSA), the COVID-19 pandemic and response has posed a challenge for HIV prevention, testing, and treatment. We used routinely collected President's Emergency Plan for AIDS Relief (PEPFAR) Monitoring, Evaluation, and Reporting (MER) data to assess potential loss to follow-up (LTFU) across PEPFAR countries in SSA before and during the pandemic to determine the impact of COVID-19 on HIV clinical treatment.

**Methods:** Treatment and LTFU data for people living with HIV (PLHIV) aged 15+ from Oct – Dec 2019 (fiscal year[FY]20 quarter[Q]1; pre-COVID) and Apr – Jun 2020 (FY20Q3; during COVID-19) were extracted from two MER indicators: TX\_CURR (PLHIV on treatment) and TX\_ML (tracking outcomes of PLHIV potentially LTFU) for 18 countries in SSA. Aggregate indicator data are not linked. Data were disaggregated by age band (15–19, 20–29, 30–39, 40–49, 50+) and sex. Proportions of potential LTFU were calculated as total number of PLHIV with no known clinical contact since last expected contact divided by total PLHIV on treatment during the reporting quarter. Proportions of select outcomes of potential LTFU (Died, LTFU <3 months since last expected clinical contact, LTFU ≥3 months since last expected clinical contact) were calculated as total individual outcome divided by total LTFU. Analyses were disaggregated by reporting quarter, age band, and sex and paired t-tests were run to test for statistical significance between quarters.

**Results:** Number of PLHIV LTFU was 644,380 in FY20Q1 and 740,112 in FY20Q3 across the 18 countries. Proportion of any LTFU outcome was 4.9% and 5.3% for the two quarters, respectively, and was higher overall among men and those aged 20–29, although not statistically significant (Table). Among all LTFU, an increase in deaths and in LTFU ≥3 months among men and a decrease in LTFU <3 months among women and all age bands were statistically significant.

**Conclusion:** The proportion of LTFU <3 months decreased during the early months of the COVID-19 pandemic in SSA, which, in part, may be attributed to adaptations in HIV programming implemented to mitigate further transmission of COVID-19. These data give an initial indication that the COVID-19 pandemic may have implications for HIV treatment in the coming months and ongoing data review is critical.

Table. Total number and proportion of PLHIV on ART treatment, potential lost to follow-up (LTFU), and disaggregated reasons for LTFU by quarter, sex, and age group – 18 countries, sub-Saharan Africa, FY20Q1 and FY20Q3\*

|                  | FY20Q1             |                          |                       |                      |                      | FY20Q3             |                          |                       |                      |                      |
|------------------|--------------------|--------------------------|-----------------------|----------------------|----------------------|--------------------|--------------------------|-----------------------|----------------------|----------------------|
|                  | On ART Treatment n | All potential LTFU n (%) | Documented died n (%) | LTFU <3 months n (%) | LTFU ≥3 months n (%) | On ART Treatment n | All potential LTFU n (%) | Documented died n (%) | LTFU <3 months n (%) | LTFU ≥3 months n (%) |
| <b>Sex</b>       |                    |                          |                       |                      |                      |                    |                          |                       |                      |                      |
| Male             | 4,307,646          | 278,301 (6.5)            | 12,134 (4.4)*         | 29,277 (10.5)        | 129,828 (46.7)*      | 4,603,118          | 253,130 (5.5)            | 12,814 (5.1)*         | 20,143 (8.0)         | 171,924 (67.9)*      |
| Female           | 8,823,873          | 424,483 (4.8)            | 14,169 (3.3)          | 50,589 (11.9)*       | 250,985 (59.3)       | 9,325,835          | 486,982 (5.2)            | 14,289 (2.9)          | 35,503 (7.3)*        | 335,520 (68.9)       |
| Total            | 13,131,519         | 644,380 (4.9)            | 26,303 (4.1)          | 79,866 (12.4)*       | 380,813 (59.3)       | 13,928,953         | 740,112 (5.3)            | 27,103 (3.7)          | 55,646 (7.5)*        | 507,444 (68.6)       |
| <b>Age group</b> |                    |                          |                       |                      |                      |                    |                          |                       |                      |                      |
| 15-19            | 393,794            | 23,022 (6.9)             | 562 (2.4)             | 3,620 (15.3)*        | 13,428 (56.9)        | 354,425            | 23,351 (6.6)             | 553 (2.4)             | 2,672 (11.4)*        | 14,938 (64.0)        |
| 20-29            | 2,145,948          | 169,971 (7.9)            | 3,636 (2.1)           | 25,771 (15.2)*       | 98,077 (57.2)        | 2,233,241          | 173,688 (7.8)            | 3,397 (2.0)           | 18,750 (10.8)*       | 113,118 (65.3)       |
| 30-39            | 4,357,991          | 223,907 (5.3)            | 7,630 (3.4)           | 27,586 (12.3)*       | 133,317 (59.5)       | 4,447,217          | 255,977 (5.8)            | 7,500 (2.9)           | 19,347 (7.6)*        | 177,852 (69.5)       |
| 40-49            | 3,753,961          | 141,236 (3.8)            | 1,121 (0.0)           | 14,911 (10.6)*       | 85,464 (60.5)        | 4,006,824          | 173,772 (4.3)            | 1,263 (0.7)           | 9,634 (5.5)*         | 123,207 (10.9)       |
| 50+              | 2,629,825          | 85,644 (3.3)             | 7,354 (8.6)           | 7,978 (9.3)*         | 50,527 (59.0)        | 2,888,246          | 113,324 (3.9)            | 8,370 (7.4)           | 5,263 (4.6)*         | 78,029 (68.9)        |
| Total            | 13,131,519         | 644,380 (4.9)            | 26,303 (4.1)          | 79,866 (12.4)        | 380,813 (59.3)       | 13,928,953         | 740,112 (5.3)            | 27,103 (3.7)          | 55,646 (7.5)*        | 507,444 (68.6)       |

\*Proportion of all potential LTFU was calculated as number of PLHIV with no known clinical contact since last expected contact divided by all PLHIV on treatment during the reporting quarter. Proportion of reasons for LTFU was calculated as number of PLHIV LTFU by disaggregate reason divided by all LTFU. LTFU reasons of refusal or transfers were not included; thus, proportions of included reasons for LTFU do not equal 100.0. All calculations represent row proportions.

\*Statistical significance at p < 0.05.

**739 IMPACT OF COVID-19 ON COMMERCIAL LABORATORY TESTING FOR HIV IN THE UNITED STATES**

**Kevin P. Delaney<sup>1</sup>**, Praveena Jayanthi<sup>2</sup>, Brian Emerson<sup>1</sup>, Weiming Zhu<sup>1</sup>, Marc A. Pitasi<sup>1</sup>, Ya-Lin A. Huang<sup>1</sup>, Kathleen P. Hartnett<sup>1</sup>, Karen W. Hoover<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>ICF International, Atlanta, GA, USA

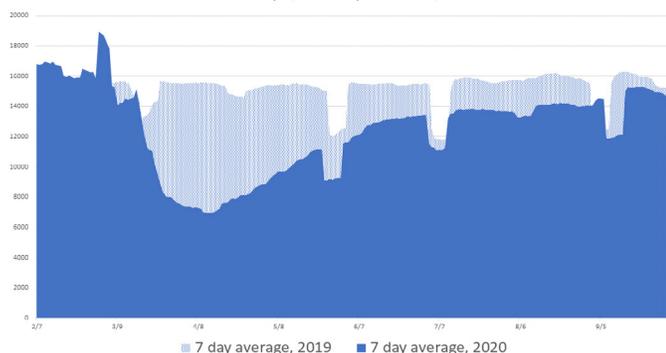
**Background:** On March 13, 2020, the United States declared a national emergency to combat coronavirus disease 2019 (COVID-19). Many states and localities issued shelter-in-place or stay-at-home orders to reduce the spread of COVID-19, limiting movement outside the home to essential activities. Since that time the pandemic has been associated with documented disruptions in routine preventive and other nonemergency care. Screening for HIV infections as well as HIV-1 viral load monitoring for persons living with HIV have likely been affected by the pandemic. Laboratory data from the National Syndromic Surveillance Program provide one way to assess the impact of the COVID-19 pandemic on HIV screening, HIV diagnoses and HIV-1 viral load monitoring.

**Methods:** Using data reported daily to CDC from a large commercial laboratory, we identified lab test reports for HIV screening or HIV-1 viral load testing. For reports with HIV screening test results, we assessed how often the final HIV test algorithm result was confirmed positive. We plotted daily counts of each of the three HIV test types and 7-day moving averages. We also calculated the difference in the number of each type of test performed between March 13, 2019 and September 30, 2019 from those performed during the same time period in 2020.

**Results:** Compared with number of tests performed in 2019, there were 669,847 fewer HIV screening tests, 4,910 fewer confirmed HIV-1 diagnoses, and 67,694 fewer HIV-1 viral load tests performed during March 13 to September 30, 2020. The 7-day average number of HIV tests performed dropped dramatically after March 13, 2020 and did not recover to 2019 levels by September 30, 2020 (Figure).

**Conclusion:** During the national COVID-19 emergency, routine screening for HIV and HIV-1 viral load monitoring may have been delayed or foregone by many patients and clinicians. Undiagnosed HIV infection and higher viral loads could have led to increased morbidity and transmission. Although the number of tests being performed has partially recovered from a nadir this spring, testing at this commercial lab has not yet rebounded to make up what was lost. Healthcare system adaptations including home testing, home sample collection, and telemedicine visits for HIV care can help to address this shortfall as the COVID-19 pandemic persists in the US.

Figure: Seven day moving average of total HIV Ag/AB screening tests performed by day: February 1, 2019-September 30, 2019, compared to February 1, 2020-September 30, 2020



#### 740 PROJECT CoRECT (COOPERATIVE REENGAGEMENT CLINICAL TRIAL): FINAL CONNECTICUT RESULTS

**Merceditas Villanueva**<sup>1</sup>, Janet Miceli<sup>1</sup>, Constance Carroll<sup>1</sup>, Suzanne Speers<sup>2</sup>, Lisa Nichols<sup>1</sup>, Heidi Jenkins<sup>2</sup>, Frederick Altice<sup>1</sup>

<sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>Connecticut Department of Public Health, Hartford, CT, USA

**Background:** The CDC sponsored Cooperative Re-Engagement Controlled Trial (CoRECT) tested a Data to Care (D2C) strategy that was based on a collaborative approach between health departments and HIV clinics to identify, re-engage, retain and virally suppress persons with HIV (PWH) who were recently out-of-care (OOC). CT was one of 3 sites that participated in this first randomized control trial (RCT) to test efficacy of this approach.

**Methods:** The CT DPH, Yale University School of Medicine and 23 HIV clinics conducted the study. Using the DPH eHARS surveillance database and individual clinic level data, PWH defined as OOC (lack of HIV VL and/or clinic visits 6 months after a 1 year in-care period) were investigated by clinic personnel to assess eligibility for randomization to clinic standard of care (SOC) vs DPH field epidemiologists (DIS or disease intervention specialists) who were trained to locate, assess barriers to care, and facilitate re-linkage to care. Primary outcomes were: re-engagement at 90 days, retention in HIV care at 12 months, viral suppression (VS) at 12- and 18-months post randomization.

**Results:** There were 655 patients randomized: DIS (N=333) vs. SOC (N=322), mean age was 46.1 years; 62.4% were male; 37% were Hispanic, 40.3% were black, 20.8% white; 29.6% MSM; 27.2% IDU; 29% heterosexual; there was no significant difference between the 2 arms. For primary outcomes: re-engagement at 90 days, DIS 170 (51.1%) vs SOC 135 (41.9%),  $p=0.019$ ; retention in care at 12 months, DIS 167 (50.2%) vs SOC 157 (48.8%),  $p=0.72$ ; VS at 12 months, DIS 213 (78%) vs SOC 187 (70.8%),  $p=0.561$ ; VS at 18 months, DIS 221

(66.4%) vs SOC 205 (63.7%),  $p=0.47$ . PWH who were re-engaged in care at 90 days (either DIS or SOC) were more likely to be retained at 12 months,  $p<0.001$ .

**Conclusion:** 1) A Data to Care process involving active input from HIV clinics in collaboration with CT DPH successfully identified recently OOC clients by a joint data sharing and case evaluation process 2) The DIS intervention was successful in re-engaging OOC PWH at 90 days but not in longer term outcomes such as retention in care at 12 months and VS at 12 and 18 months. 3) Re-engagement in care at 90 days was associated with increased likelihood of retention at 12 months 4) For this recently OOC group, there remain gaps in all primary outcomes, suggesting that additional interventions are needed 5) The D2C approach created a working relationship between DPH and HIV clinics which is key to improvements in local HIV care cascades

#### 741 IMPACT OF COVID-19 PANDEMIC ON HIV CARE IN BRAZIL

**Ana Roberta P. Pascom**<sup>1</sup>, Nazle Veras<sup>1</sup>, Rosana Elisa G. Pinho<sup>1</sup>, Isabela O. Pereira<sup>1</sup>, Lais M. Aquino<sup>1</sup>, Marcelo A. De Freitas<sup>2</sup>, Gerson Fernando M. Pereira<sup>1</sup>

<sup>1</sup>Ministry of Health, Brasilia, Brazil, <sup>2</sup>Pan-American Health Organization, Brasilia, Brazil

**Background:** In March 2020, the Brazilian Ministry of Health (MoH) announced COVID-19 countrywide community transmission and issued guidelines on social distancing measures. Using real life data, we aimed to analyze the impact of COVID-19 on HIV care in Brazil, and summarize the actions taken by the MoH to guarantee proper health care for people living with HIV (PLWHIV).

**Methods:** We obtained MoH electronic records, from January-October 2019/2020, on HIV self test (HIVST), viral load (VL), CD4+ T counts (CD4), genotyping, and antiretroviral (ART) prescription, including post- (PEP) and pre-exposure (PrEP) prophylaxis. We used descriptive statistics to quantify COVID-19 impact on HIV care in Brazil and compared indicators of both years by unpaired T-tests.

**Results:** In April 2020, PEP and PrEP dispenses fell 57% and 53%, respectively, when compared to January, and new PrEP users dropped 70%. Four months supplies provision and telemedicine resulted on 64% and 53% increase on PEP and PrEP dispenses and 288% rise on new PrEP users in October, when compared to April. The number of HIVST distributed by MoH and PLWHIV who had the first CD4 and VL before ART initiation dropped 35% and 48%, respectively, when comparing April to January 2020, reflecting the pandemic impact on HIV diagnosis. In return, MoH recommended HIVST for key/priority populations, pregnant women, patients with TB, STI, viral hepatitis, immunosuppressed, or hospitalized due to respiratory syndrome. When comparing to April, HIVST distribution raised 95% in October and the number of PLWHIV who had the first CD4 and VL before ART initiation was 56% higher, in September. When comparing 2020 to 2019, the number of PLWHIV who started ART and those that had the first CD4 and VL before ART initiation was 29% and 48% lower in April 2020, respectively; but 18% and 15% in September. Considering January-October, the proportion of PLWHIV overdue for ART dispensation raised 11% and ART dispense for 30 days dropped 53% in 2020; but increased 27% and 105%, for 60 and 90 days, respectively. The use of telemedicine, annual VL for those clinically stables, and 90-days ART supply held link to public health services and viral load suppression.

**Conclusion:** PLWHIV are vulnerable during COVID-19 pandemic due to compromised immune system or care continuum interruption by community containment measures. Monitoring of HIV care indicators associated to timely actions is an effective way to overcome COVID-19 pandemic challenges and guarantee proper health care for PLWHIV

#### 742 HOME SPO2 MONITORING OF PATIENTS WITH COVID-19: THE MATER CVC PROJECT

**Stephen P. Connolly**<sup>1</sup>, Henriette Wa Katolo<sup>1</sup>, Colm Cronin<sup>1</sup>, Maria Creed<sup>1</sup>, John S. Lambert<sup>1</sup>, Aoife G. Cotter<sup>1</sup>, Eavan G. Muldoon<sup>1</sup>, Gerard Sheehan<sup>1</sup>, Heather Coetzee<sup>1</sup>, Alan Sharpe<sup>1</sup>, Eileen O'Connor<sup>1</sup>, Jeremy Farrell<sup>1</sup>, Aoife Heeney<sup>1</sup>, Suzanne Dempsey<sup>1</sup>, Tara McGinty<sup>1</sup>

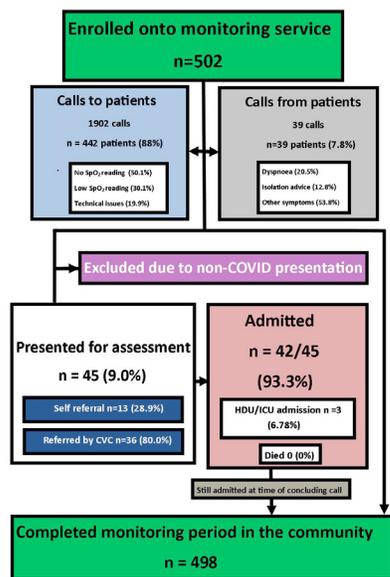
<sup>1</sup>Mater Misericordiae University Hospital, Dublin, Ireland

**Background:** The COVID19 pandemic has necessitated innovative ways to provide safe healthcare remotely for large numbers of infected patients. We implemented a COVID Virtual Clinic (CVC) in a tertiary referral centre allowing such patients to be monitored in the community. This study describes the CVC's remote monitoring experience and explores the predictors of need for specialist intervention.

**Methods:** We included all patients enrolled in the CVC at the Mater Misericordiae University Hospital, Dublin between March 1st and June 1st 2020. Patients received a Bluetooth-enabled pulse oximeter and smartphone application (Patient-M-Power®) and uploaded twice-daily SpO<sub>2</sub> readings, heart rate and dyspnoea score (1-10). A team of 2-14 healthcare providers monitored results. Abnormal or absent data triggered calls from the CVC, with assessments and/or admission as required. We collected data on demographics, calls received from/made to patients, outcomes and readmissions. Descriptive analysis of the CVC was performed as well as simple logistic regression to explore factors associated with the likelihood of readmission.

**Results:** 502 patients were included (179 (36.4%) male, median age 39 (IQR 50-3) years, 360 (73.2%) staff). Outcomes are illustrated in Figure 1. Median time in CVC was 12 days (IQR 13-10). 1902 calls were made to patients by CVC staff prompted by abnormal data: dyspnoea (41 patients, 8.2%), low SpO<sub>2</sub> (133, 26.5%), tachycardia, (99, 19.7%), technical issues (81, 16.1%), absent results (255, 50.1%). This resulted in 45 (9%) patients requiring re-assessment and 42 (8.4%) being readmitted. Of those readmitted, 3 (7%) required critical care admission. Median length of stay was 2 (IQR 6.75-1) days. Those readmitted were more likely to be older (odds ratio [OR] per year older 1.03 (1.01, 1.05), P=0.0050, have an abnormal SpO<sub>2</sub> (<94%, OR 5.43 [2.93, 11.1], P<0.001), a high dyspnoea score (>7, OR 4.33 (2.04, 9.3), P<0.001) and be staff (OR 6.08 (3.11, 11.87), P<0.001). Neither gender nor abnormal HR were associated with higher likelihood of readmission. 22.2% of presenting patients were hypoxic in the absence of dyspnoea, of which 70% required admission and one patient required intensive care.

**Conclusion:** We describe the largest remotely monitored cohort of COVID19 patients to date. The low frequency of readmissions and value of SpO<sub>2</sub> monitoring and dyspnoea scores as predictors of readmission highlights the value of this model in providing safe care whilst minimising unnecessary admissions.



#### 743 CHANGES IN ACCESS TO CARE FOR WOMEN LIVING WITH HIV DURING THE COVID-19 PANDEMIC

**Caitlin Bernard**<sup>1</sup>, John M. Humphrey<sup>2</sup>, Julie Thorne<sup>3</sup>, Shukri Hassan<sup>4</sup>, Victor Omodi<sup>5</sup>, Beatrice Jakait<sup>5</sup>, Kara Wools-Kaloustian<sup>1</sup>, Rena Patel<sup>4</sup>, Mercy Maina<sup>6</sup>  
<sup>1</sup>Indiana University, Indianapolis, IN, USA, <sup>2</sup>Indiana University, Bloomington, IN, USA, <sup>3</sup>University of Toronto, Toronto, Canada, <sup>4</sup>University of Washington, Seattle, WA, USA, <sup>5</sup>Academic Model Providing Access to Healthcare, Eldoret, Kenya, <sup>6</sup>Moi Teaching and Referral Hospital, Eldoret, Kenya

**Background:** The COVID-19 pandemic has disrupted health services globally. We examined the self-reported impact of the pandemic on access to HIV and family planning (FP) services among women living with HIV (WLHIV) at a large HIV treatment program in Kenya.

**Methods:** Telephone surveys were conducted among a non-random, purposeful sample of WLHIV ≥15 years of age exposed to dolutegravir (DTG) at HIV clinics affiliated with the Academic Model Providing Access to

Healthcare (AMPATH), a PEPFAR-supported treatment program in western Kenya. Participants completing phone interviews for a DTG-focused study named Chaguo Langu were asked structured questions about their HIV and FP experiences and pregnancy intentions in the context of the pandemic. Multivariable logistic models were used to estimate the odds of self-reported difficulty refilling medications and obtaining care, respectively, adjusted for age, partner status, number of children, time on ART, and HIV clinic site. **Results:** Among 814 women called from June-October 2020, 784 (96%) completed the survey. Overall, 14% reported experiencing increased difficulty obtaining care during the pandemic, primarily due to cost or unavailability of transportation (61%). Further, 32% reported increased difficulty refilling medications during the pandemic, primarily due to medication stock-outs (79%). However, only 2% reported missing medication doses. Only 2% reported increased difficulty managing (including initiating, refilling, and removing) FP methods, primarily due to stock-outs of implants and injectables (69%). Most (95%) reported no impact of the pandemic on their intentions to use FP or become pregnant. None of the factors assessed in the multivariable model were associated with difficulty obtaining care. Older women were less likely (aOR=0.95, 95% CI: 0.92-0.98), and women with a higher number of children were more likely (aOR=1.13, 95% CI: 1.00-1.28) to have an association with difficulty refilling medications.

**Conclusion:** A significant proportion of WLHIV report experiencing greater difficulty obtaining HIV care and medication refills during the pandemic, while women's ability to manage FP during the pandemic largely remained stable. Addressing medication stock-outs and transportation challenges may help HIV programs in resource-constrained settings ensure that access to HIV and FP services is not disrupted during the COVID-19 pandemic. As the pandemic continues, FP access and use should continue to be monitored to avoid unintended pregnancies.

**Table 1. Characteristics of participants and key outcomes of telephone survey completed by women living with HIV about changes in access to HIV and family planning (FP) care during the COVID-19 pandemic (N=784).**

| Characteristic/Outcome                      | N (%) or median (IQR) |
|---|-----------------------|
| Age, years                                  | 37 (28-42)            |
| Married or cohabitating (n=774)             | 436 (56)              |
| Number of living children                   | 2 (1-3)               |
| Attends HIV clinic at MTRH <sup>a</sup>     | 273 (35)              |
| Time on ART, years                          | 9 (4-12)              |
| Use of family planning <sup>b</sup> (n=763) | 649 (83)              |
| Dolutegravir as ART <sup>c</sup> base       | 520 (66)              |
| Difficulty refilling medications            | 249 (32)              |
| Difficulty obtaining medical care           | 107 (14)              |
| Difficulty managing family planning         | 16 (2)                |

<sup>a</sup>MTRH: Moi Teaching and Referral Hospital (quaternary referral center in western Kenya)

<sup>b</sup>Includes condoms, sterilization, contraceptive implant, intrauterine contraceptive device, injectable, oral, and natural family planning methods

<sup>c</sup>ART: antiretroviral treatment

#### 744 BARRIERS IMPACTING TELEHEALTH MEDICAL-APPOINTMENT ADHERENCE AMONG PLWHA

**Nicole Ennis**<sup>1</sup>, Laura Armas<sup>2</sup>, Seyram Butame<sup>1</sup>

<sup>1</sup>Florida State University, Tallahassee, FL, USA, <sup>2</sup>CAN Community Health, Sarasota, FL, USA

**Background:** Access to medical treatment and care for those living with or at risk for HIV is vital to ensuring quality of life and limiting the spread of the disease. Lack of access to medical care is associated with poor disease management, antiretroviral medication failure, and increased incidence of ER visits and/or hospitalizations. To address the medical care needs of patients living with HIV providers have adapted to telehealth protocols that have allowed them to examine, assess and treat patients using secure 2-way video platforms with audio capabilities. While telehealth has been successfully implemented for patients in routine care, lack of access due to the digital divide has not been closely examined. The goal of the current study was to characterize the response of patients to telehealth during the first six months of active telehealth care.

**Methods:** Due to COVID-19 pandemic CAN community clinics transitioned to video telehealth visits. Appointment adherence data for this study was taken from the electronic health record appointment using April 1, 2020-October 31, 2020 timeframe. No shows, cancellations and rescheduled appointments were excluded.

**Results:** We identified 5,470 unique patients who completed a total of 12,345 visits at CAN community locations, 80% of clinics were located in Florida. The average age of the population 48.62 yrs with SD of 13.37 yrs with range of 16

yr-88 yrs. 88% of patients had a confirmed HIV diagnosis and 12% of patients were on PrEP, majority (78%) identify as male, 62% identify as MSM, and 60% identified as White. Descriptive analysis shows that Blacks were 15% and those who identify as heterosexual were 24% more likely to have failed telehealth appointments (FT). FT decreased as in-person (IP) appointments increased. Apr (FT 48% v. IP 5%) May (FT 53% v. IP 4%); Jun (FT 32% v. IP 7%); Jul (FT 30% v. IP 8%); Aug (FT 28% v. IP 13%); Sept (FT 15% v. IP 28%); Oct (FT 8% v. IP 50%).

**Conclusion:** Currently, approximately three-in-ten adults with household incomes below \$30,000 a year don't own a smartphone and more than four-in-ten don't have home broadband services (44%) or a computer (46%). Those who often have the most to gain from telehealth approaches are also the least likely to have access to broadband and/or cannot afford the necessary technology to engage in 2 way video telehealth appointments. Our work demonstrates that to serve the most vulnerable populations living with HIV more needs to be done to address the digital divide.

**Table 01 – Demographics: Patients attending CAN Clinics, April 2020 – October 2020 (N = 5470; All encounters = 12345)**

|                               | Video Health Visit (%) | Phone Health Visit (%) | In-Person Visit (%) | All Visit Formats (%) |
|-------------------------------|------------------------|------------------------|---------------------|-----------------------|
| <b>Sex</b>                    |                        |                        |                     |                       |
| Female                        | 1223 (19.97)           | 886 (29.82)            | 456 (23.85)         | 2565 (23.31)          |
| Male                          | 4900 (80.03)           | 2085 (70.18)           | 1450 (75.84)        | 8435 (76.64)          |
| Unknown                       | 0 (0.00)               | 0 (0.00)               | 6 (0.31)            | 6 (0.05)              |
| <b>Gender</b>                 |                        |                        |                     |                       |
| Female                        | 1123 (18.65)           | 852 (29.27)            | 435 (23.30)         | 2410 (22.32)          |
| Male                          | 4711 (78.26)           | 2006 (68.91)           | 1362 (72.95)        | 8079 (74.82)          |
| Transgender Female            | 100 (1.66)             | 33 (1.13)              | 55 (2.95)           | 188 (1.74)            |
| Transgender Male              | 32 (0.53)              | 1 (0.03)               | 2 (0.11)            | 35 (0.32)             |
| Genderqueer                   | 18 (0.30)              | 1 (0.03)               | 6 (0.32)            | 25 (0.23)             |
| Other/No Response             | 36 (0.60)              | 18 (0.62)              | 7 (0.37)            | 61 (0.56)             |
| <b>Sexual Orientation</b>     |                        |                        |                     |                       |
| Lesbian/gay/homosexual        | 3732 (62.15)           | 1145 (39.65)           | 812 (43.54)         | 5689 (52.89)          |
| Heterosexual                  | 1677 (27.53)           | 1500 (51.96)           | 721 (38.66)         | 3898 (36.24)          |
| Bisexual                      | 306 (5.13)             | 112 (3.88)             | 111 (5.95)          | 531 (4.94)            |
| Other                         | 52 (0.87)              | 15 (0.52)              | 26 (1.39)           | 93 (0.86)             |
| Don't know/No response        | 236 (3.93)             | 115 (3.98)             | 195 (10.46)         | 546 (5.08)            |
| <b>Race</b>                   |                        |                        |                     |                       |
| Black/African America         | 1507 (24.75)           | 1160 (39.11)           | 837 (43.80)         | 3504 (31.95)          |
| American Indian/Alaska        | 5 (0.08)               | 1 (0.03)               | 2 (0.10)            | 8 (0.07)              |
| Asian                         | 57 (0.94)              | 22 (0.74)              | 16 (0.84)           | 95 (0.87)             |
| Native Hawaiian/Pacific       | 48 (0.79)              | 27 (0.91)              | 16 (0.84)           | 91 (0.83)             |
| White                         | 3671 (60.39)           | 1360 (45.52)           | 808 (42.58)         | 5839 (53.21)          |
| Other                         | 458 (7.52)             | 259 (8.73)             | 127 (6.65)          | 844 (7.70)            |
| No response                   | 337 (5.53)             | 147 (4.95)             | 105 (5.49)          | 589 (5.37)            |
| <b>Ethnicity</b>              |                        |                        |                     |                       |
| Not Hispanic/Latino           | 4592 (76.20)           | 2260 (76.56)           | 1512 (80.34)        | 8364 (77.02)          |
| Hispanic/Latino               | 906 (15.03)            | 420 (14.23)            | 225 (11.96)         | 1551 (14.28)          |
| No Response                   | 528 (8.76)             | 272 (9.21)             | 145 (7.70)          | 945 (8.70)            |
| <b>HIV Status/Prep Status</b> |                        |                        |                     |                       |
| HIV Negative (On PrEP)        | 974 (15.91)            | 117 (3.94)             | 225 (11.77)         | 1316 (11.96)          |
| HIV Positive (Not on PrEP)    | 5149 (84.09)           | 2854 (96.06)           | 1687 (88.23)        | 9590 (88.04)          |
| <b>Viral Load</b>             |                        |                        |                     |                       |
| Undetectable                  | 4828 (78.85)           | 147 (4.95)             | 1218 (63.70)        | 8593 (78.08)          |
| Detectable                    | 1295 (21.15)           | 424 (14.27)            | 694 (36.30)         | 2413 (21.92)          |
| <b>Mean</b>                   | 46.91; SD=12.36;       | 52.90; SD=12.61;       | 47.74; SD=14.28;    | 46.62; SD=13.37;      |
| <b>Median</b>                 | 48; Range: 17-85       | 55; Range: 20-88       | 50; Range: 16-88    | 51; Range: 16-88      |

**745 COVID-19 IMPACT ON THE COST OF INDEX TESTING HIV CASE DETECTION IN 5 INDIAN DISTRICTS**

**Salin Sriudomporn**<sup>1</sup>, Rose Pollard<sup>2</sup>, Gincy Thomas<sup>3</sup>, Aylur Kailasam Ganesh<sup>3</sup>, Ajay K. Enugu<sup>2</sup>, Subash Ghosh<sup>2</sup>, Aditya Singh<sup>2</sup>, Jalpa Thakkar<sup>2</sup>, Sunil S. Solomon<sup>2</sup>, Bryan Patenaude<sup>1</sup>

<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>YR Gaitonde Center for AIDS Research and Education, Chennai, India

**Background:** Index testing is a viable strategy to identify HIV cases globally and is a cornerstone of all PEPFAR programs. COVID-19 and associated lockdowns impacted access to health services including HIV testing. The financial impact of these lockdowns on HIV case detection has not been studied in-depth.

**Methods:** Program ACCELERATE implemented Facility-Based Index Testing (FBIT; n=5 districts) and Community-Based Index Testing (CBIT; n=3 districts) in 2 high-burden Indian states. Retrospective costing data were obtained from expenditure records, including cost of labor, supplies/equipment, capital, training, and operational costs. Fixed and recurrent costs at the programmatic level, both overall and per district, were estimated, excluding the cost of HIV testing. On 03/24/2020, India implemented a nationwide lockdown. 10/2019-03/2020 was classified as pre-COVID and 04/2020-09/2020 as post-COVID. To derive the unit cost per individual, the number of clients offered and accepted index testing, contacts elicited, contacts who accepted and completed HIV testing, contacts who tested positive, and new PLHIV initiated on ART were retrieved for each district.

**Results:** The total programmatic cost to implement FBIT pre-COVID was \$265,061, which reduced by 21.5% to \$207,333 post-COVID, including startup cost for both periods. The cost to implement CBIT reduced by 63% from \$160,851 to \$59,605, pre and post pandemic. Pre-COVID, labor accounted for 77% of the overall implementation cost vs. 90.3% post-COVID. The total number of contacts who tested positive over 6 months of FBIT implementation reduced by 65.3% pre- to post-COVID (1048 vs 364) and by 30.6% (399 vs 277) for CBIT. Newly diagnosed PLHIV initiated on ART declined by 65.1% (895 vs 312) for FBIT and by 19.3% (311 vs 251) for CBIT. Across all districts implementing FBIT, the cost per new HIV diagnosis increased from \$253 to \$728, and for CBIT, from \$403 to \$581. The per unit cost of PLHIV initiated on ART for FBIT increased from \$296 to \$850, and for CBIT, from \$517 to \$641.

**Conclusion:** The average pre-COVID cost per new HIV diagnosis through FBIT among 5 Indian districts is below the estimated cost in most LMICs. Post-COVID, the cost per diagnosis and ART initiation almost tripled for FBIT, primarily driven by a lower volume of cases. Innovative strategies, such as integrating home-based testing and HIV-self testing, may be required to offset travel restrictions imposed by COVID-19 and improve program efficiency, while minimizing exposure to SARS-CoV-2.

**Table 1. Index testing cascade totals and cost per individual across all locations pre- and post-COVID**

|   | Overall                         |                                 | FBIT                            |                                 | CBIT                           |                                 |
|---|---------------------------------|---------------------------------|---------------------------------|---------------------------------|--------------------------------|---------------------------------|
|   | Pre-COVID                       | Post-COVID                      | Pre-COVID                       | Post-COVID                      | Pre-COVID                      | Post-COVID                      |
| Number of clients offered index testing services      | n = 4717 (\$90.29 per client)   | n = 887 (\$300.94 per client)   | n = 4194 (\$63.20 per client)   | n = 736 (\$360.14 per client)   | n = 523 (\$307.55 per client)  | n = 151 (\$1,065.24 per client) |
| Number of clients who accepted index testing services | n = 4199 (\$101.43 per client)  | n = 851 (\$313.68 per client)   | n = 3956 (\$71.72 per client)   | n = 709 (\$378.66 per client)   | n = 503 (\$319.78 per client)  | n = 151 (\$1,065.24 per client) |
| Number of contacts who accepted HIV testing           | n = 5816 (\$73.23 per contact)  | n = 2290 (\$119.1 per contact)  | n = 4139 (\$64.94 per contact)  | n = 1362 (\$194.91 per contact) | n = 1677 (\$95.92 per contact) | n = 898 (\$179.12 per contact)  |
| Number of contacts who completed HIV testing          | n = 5480 (\$77.72 per contact)  | n = 2207 (\$120.95 per contact) | n = 3803 (\$69.70 per contact)  | n = 1318 (\$201.11 per contact) | n = 1677 (\$95.92 per contact) | n = 889 (\$180.93 per contact)  |
| Number of contacts who tested positive                | n = 1447 (\$294.34 per contact) | n = 641 (\$416.44 per contact)  | n = 1048 (\$252.92 per contact) | n = 364 (\$728.19 per contact)  | n = 399 (\$403.13 per contact) | n = 277 (\$580.69 per contact)  |
| Number of new PLHIV initiated on ART                  | n = 1206 (\$335.16 per contact) | n = 583 (\$474.14 per contact)  | n = 895 (\$296.16 per contact)  | n = 312 (\$849.55 per contact)  | n = 311 (\$517.20 per contact) | n = 251 (\$640.94 per contact)  |

**746 SYNDROMIC SURVEILLANCE FOR COVID-19 AND HEALTH CARE ACCESS AMONG ART PATIENTS, MALAWI**

**Thulani Maphosa**<sup>1</sup>, Thoko K. Kalua<sup>2</sup>, Brittney N. Baack<sup>3</sup>, Evelyn Kim<sup>3</sup>, Joram L. Sunguti<sup>1</sup>, Anne Chauma-Mwale<sup>4</sup>, Rhoderick Machekeano<sup>5</sup>, Alice N. Maida<sup>3</sup>, Andrew S. Azman<sup>6</sup>, Andrew F. Auld<sup>3</sup>, Suzgo Zimba<sup>1</sup>, Harrid Nkhoma<sup>1</sup>, Rachel Kanyenda<sup>1</sup>, Rose Nyiranda<sup>2</sup>, Godfrey Woelk<sup>5</sup>

<sup>1</sup>Elizabeth Glaser Pediatric AIDS Foundation, Lilongwe, Malawi, <sup>2</sup>Department of HIV and AIDS, Lilongwe, Malawi, <sup>3</sup>Center for Disease Control and Prevention, Lilongwe, Malawi, <sup>4</sup>Public Health Institute Malawi, Lilongwe, Malawi, <sup>5</sup>Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, USA, <sup>6</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** While little is known about the interaction of HIV and SARS-CoV-2, disruptions caused by the COVID-19 pandemic may impact the ability of people living with HIV (PLHIV) to access antiretroviral therapy (ART). We conducted syndromic surveillance to identify challenges in PLHIV's access to health care services in selected districts in Malawi.

**Methods:** We conducted telephone-based syndromic surveillance among randomly selected PLHIV ≥18 years old who had a telephone number on file in 179 ART clinics across nine districts. Patients who answered the phone were asked to verify their identity and provide consent. Staff used a structured questionnaire to collect self-reported data on demographic characteristics, experience of COVID-19 symptoms (CS) within the past 14 days as defined by the World Health Organization, access to health services, and ART interruptions (≥1 dose missed in past week) during the pandemic. We summarized data using proportions and medians and used Chi-square tests to examine associations.

**Results:** From August-October 2020, we dialed 17,944 numbers; 26.1% (4,680) confirmed their identity, were on ART and were ≥18 years. Most (93.7%, n=4,385) eligible clients consented, and 98.6% (n=4323) completed interviews. Over half (53.8%) were female. The male median age was 42 years (interquartile range [IQR] 18 – 78) compared to 36 (IQR 18 – 80) among females. Of 263 (6.1%) reporting at least one CS, persistent cough (35.7%), headache (40.3%) and fever (18.6%) were most common. Overall, 193 (4.5%) reported having been tested for SARS-CoV-2. Females were more likely to have missed school or work due to CS compared to males (37.3% vs. 21.8%, p=0.004), and were more likely to access medical care for CS (66.2% vs. 54.9%, p=0.048). Of all respondents, 17.6% reported not accessing health care services during the pandemic. Challenges included health facility closures (13.6%), no money for transport (13.9%) and fear of COVID-19 (45%). Few respondents (1.8%) reported missing ART doses.

**Conclusion:** The telephone-based syndromic surveillance system proved to be feasible in monitoring the impact of COVID-19 among PLHIV in a resource-limited setting. PLHIV reported missing school or work due to CS and not accessing health care services, though few missed their ART doses; these findings require further research. Similar systems can be used to rapidly identify and respond to COVID-19-related challenges with health care access for people on ART.

**747 UPSCALING HIV PREEXPOSURE PROPHYLAXIS IMPLEMENTATION DURING COVID-19 PANDEMIC**

**Tamirirashie C. Mahwire<sup>1</sup>**, Nthabiseng Koloane<sup>1</sup>, Jacqueline Burgess<sup>1</sup>, Ziyanda Makaba<sup>1</sup>, Claire Serrao<sup>1</sup>, Todd Malone<sup>1</sup>, for the Provincial Departments of Health Mpumalanga KwaZulu-Natal South Africa

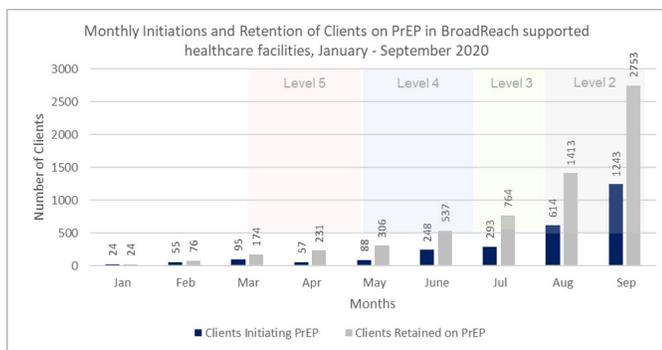
<sup>1</sup>BroadReach Corporation, Cape Town, South Africa

**Background:** HIV Pre-Exposure Prophylaxis (PrEP) was introduced in South Africa in October 2019. Low levels of PrEP uptake and retention were observed through to May 2020. The Coronavirus Disease 2019 (COVID-19) pandemic and nationwide lockdown in March 2020 contributed to additional challenges in PrEP upscale in the following ways: • Reduction in HIV Testing Services (HTS) due to facility headcount reduction and suspension of community HTS • Healthcare facility closures and/or reduction in staff after confirmed COVID-19 cases. • Suspension of in-person trainings on PrEP scheduled for March-May before all clinicians were trained • Reduction in onsite mentorship

**Methods:** After a decrease during lockdown in April, we conducted first round of virtual trainings in May. Over June-August 2020, we implemented a PrEP acceleration plan that included the following strategies: • Provision of performance targets with online coaching and mentoring for clinical staff • Virtual guidelines training of 300 clinical staff • Printing and distributing IEC materials and job aids • Integration of PrEP into HTS including HIV Self-Screening and Index testing • Stringent monitoring of PrEP drug stock and performance • NDoH-endorsed multi-month dispensing of PrEP drugs

**Results:** During lockdown, PrEP initiations decreased by 40% between March and April and following the first round of virtual trainings, increased by 182% between May and June 2020. The growth plateaued in July, before implementation of the PrEP acceleration plan which catalysed a significant growth spurt both in August of 110% (1,413/764) and in September 102% (2,753/1,413) with these two months alone accounting for 67.4% (1,857/ 2,753) of the total clients initiated since the inception of the programme.

**Conclusion:** A multi-pronged approach to manage the challenges caused by the COVID-19 pandemic succeeded in improving PrEP initiation and retention. We recommend sustained medicine availability, virtual trainings and mentorship sessions combined with PrEP/HTS integration be implemented to improve upscaling of PrEP services during a pandemic and nationwide lockdown.



**748 IMPACT OF LOCKDOWN RESTRICTIONS DUE TO COVID-19 PANDEMIC ON HIV CARE IN ITALY**

**Andrea Antinori<sup>1</sup>**, Alessandro Tavelli<sup>2</sup>, Cristina Mussini<sup>3</sup>, Andrea Gori<sup>4</sup>, Franco Maggiolo<sup>5</sup>, Antonella Castagna<sup>6</sup>, Francesca Ceccherini-Silberstein<sup>7</sup>, Sergio Lo Caputo<sup>8</sup>, Massimo Puoti<sup>9</sup>, Carmela Pinnetti<sup>1</sup>, Valeria Calvino<sup>10</sup>, Enrico Girardi<sup>1</sup>, Carlo F. Perno<sup>11</sup>, Antonella D'Arminio Monforte<sup>12</sup>, Alessandro Cozzi-Leperi<sup>13</sup>

<sup>1</sup>Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, <sup>2</sup>Icona Foundation, Milan, Italy, <sup>3</sup>University of Modena and Reggio Emilia, Modena, Italy, <sup>4</sup>Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy, <sup>5</sup>Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, <sup>6</sup>San Raffaele Vita-Salute University, Milan, Italy, <sup>7</sup>University of Rome Tor Vergata, Rome, Italy, <sup>8</sup>Universiti di Foggia, Foggia, Italy, <sup>9</sup>ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, <sup>10</sup>ANLAIDS ONLUS, Rome, Italy, <sup>11</sup>Bambino Gesù Children's Hospital, Rome, Italy, <sup>12</sup>Azienda Ospedaliera San Paolo, Milan, Italy, <sup>13</sup>Modelling and Evaluation (CREME) Institute for Global Health UCL, London, UK

**Background:** It has been observed that lockdown restrictions during COVID-19 pandemic may have had a negative impact on HIV epidemic goals with disruption in care. We aim to analyse the trends in non-viral suppression for

PLWH during and after the lockdown for COVID-19 pandemic in Italy compared to 2019.

**Methods:** We included all participants in the ICONA cohort for whom there was  $\geq 1$  viral load (VL) in the window Nov 2019-Jan 2020 and with most recent VL  $\leq 50$  copies/mL (exposed to lockdown), and over Nov 2018-Jan 2019 (not exposed). New enrolments in the study period were excluded. At population level and separately by year, we calculated proportion with VL  $\leq 50$  copies/mL at each month over March-September and we performed an intermittent time series (ARIMA) model centred in March. In addition, we defined an individual outcome using the first VL over May-September ( $>50$  vs.  $\leq 50$  copies/mL), comparing proportion with VL  $>50$  copies/mL between exposed and not exposed by means of logistic regression models. PLWH with missing VL in the outcome window were excluded from the analysis. We also performed an alternative analysis in which censoring bias was minimised using inverse probability of weighting. Sensitivity analyses were performed after restricting to clinical sites with electronic linkage with laboratory data and to the subset of PLWH under follow-up in both years.

**Results:** A total of 3,684 PLWH were included (2019=2,948; 2020=736). PLWH exposed to lockdown were significantly older, less frequently MSM, non-Italian, had a higher CD4+ count and more frequently resident in north of Italy. The mean proportion of VL  $\leq 50$  copies/mL was 97% at March 2020 (ref.), 99% before March 2020, 82% at April 2020 (ARIMA estimates -21% 95% CI: -28%; -14%; P=0.01) and 97% after April 2020. In the 2019, the same proportions were 100%, 98%, 95%, and 97% with evidence for a lower drop in April (-6%, 95% CI: -8%; -3%, p=0.02). The results of the logistic regression model are reported in Table 1. When restricting to sites with electronic VL linkage and to those followed-up in both years the IPW OR of 2020 vs. 2019 were 1.23 (0.69-2.18) and 1.03 (0.48-2.19), respectively.

**Conclusion:** We found little evidence for a difference in the proportion of PLWH with a VL  $>50$  copies/mL, following stable suppression, in the period post lockdown due to COVID-19 as compared to the previous year. Although selection bias was minimized, reasons for a missing VL should be further investigated.

|                                    | Unadjusted and adjusted OR of a VL >50 copies/mL post-lockdown |                        |         |                       |         |
|------------------------------------|--|------------------------|---------|-----------------------|---------|
|                                    | Failure n(%)   | Unadjusted HR (95% CI) | p-value | Adjusted* HR (95% CI) | p-value |
| <b>OT analysis<sup>a</sup></b>     |  |                        |         |                       |         |
| Calendar year                      |  |                        |         |                       |         |
| 2019                               | 103/2948 (3.5%)  | 1                      |         | 1                     |         |
| 2020 (exposed to lockdown)         | 22/736 (3.0%)  | 0.85 (0.53, 1.36)      | 0.499   | 0.90 (0.56, 1.44)     | 0.652   |
| <b>OT IPW analysis<sup>b</sup></b> |  |                        |         |                       |         |
| Calendar year                      |  |                        |         |                       |         |
| 2019                               |  |                        |         | 1                     |         |
| 2020 (exposed to lockdown)         |  |                        |         | 0.89 (0.56, 1.41)     | 0.610   |

<sup>a</sup>a VL >50 is counted as failures, missing VL excluded

<sup>b</sup>a VL >50 is counted as failures, censoring controlled with inverse probability of weighting (IPW)

\*adjusted for nationality, gender, geographical region of clinical site, mode of HIV transmission, pre-lockdown CD4 count, age and frequency of monitoring of VL

**Table 1. Univariable and multivariable logistic regression comparing proportion of VL >50 copies/mL in exposed (2020) and not exposed (2019) population.**

**749 INTERVENTIONS TO IMPROVE HEADCOUNT DURING COVID-19 LOCKDOWN IN SOUTH AFRICA**

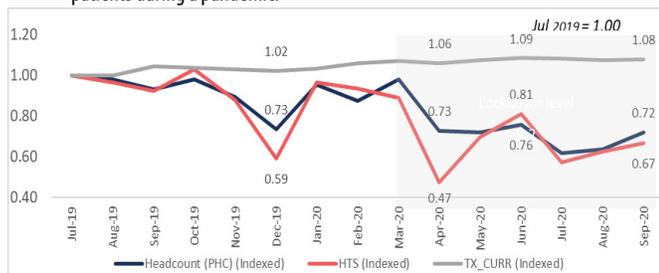
**Dhirisha Naidoo<sup>1</sup>**, Nthabiseng Koloane<sup>1</sup>, Claire Serrao<sup>1</sup>, Taryn Arthur<sup>1</sup>, Nireshni Naidoo<sup>1</sup>, Nonhlanhla Sokhulu<sup>1</sup>, Oyebola Oyebanji<sup>1</sup>, Gugu Xaba<sup>1</sup>, Ntombifkile Thekiso<sup>1</sup>, Calvin Moyana<sup>1</sup>, Todd Malone<sup>1</sup>, for the Department of Health <sup>1</sup>BroadReach Corporation, Cape Town, South Africa

**Background:** The world was overcome by the COVID-19 pandemic from late 2019. South Africa entered into a country wide lockdown level 5 from March 26 to April 16, 2020. Public health facilities were greatly affected as they experienced reduced facility headcounts, which resulted in reduced HIV testing services (HTS), reduced patients attending their follow-up visits, and this also impacted the viral load completions.

**Methods:** This was a retrospective review that analyzed the trends and the impact COVID-19 had on the headcount of primary health care (PHC) facilities and the number of patients accessing HTS and the Total Remaining on ART (TROA). In order to view the facility headcount and HTS trends on the same scale, for graphical representation the monthly figures have been indexed to their values in July 2019 (Jul 2019 = 100), prior to the impact of COVID-19 and the typical seasonal decline in activity during the holiday period.

**Results:** Facility headcount dropped during the COVID-19 period (Mar 20, 0.98 to Apr 20, 0.73); and it is clear that the HTS trends (Mar 20, 0.89 to Apr 20, 0.47) mirror the headcount trends (Figure 1). However, the total remaining on ART remained relatively stable during this period; demonstrating successful programme efforts towards retention. These activities included case management of clients, community ART delivery, SMS reminders, extension of CCMDD (Centralised Chronic Medication Dispensing and Distribution) scripts, multi-month scripting and dispensing, improved appointment systems in facilities where we had filing interns, data quality improvement activities during this period and daily tracking with the district teams. Historically we have seen that HTS habitually drops during the holiday periods of December and April but starts picking up and follows the headcount trends. This year Level-5 lockdown brought on a steep drop with a strong recovery once lockdown restrictions eased, albeit not totally to former levels.

**Conclusion:** Therefore, despite drastic drops in headcount from April 2020 to September 2020 as compared to 2019, the stability of TROA shows that implemented retention strategies have had a positive impact on the retention of patients during a pandemic.



**750 COMPARISON OF COMMUNITY TESTING OUTCOMES OVER SOUTH AFRICAN COVID-19 LOCKDOWN LEVELS**

**Jacqueline Burgess**<sup>1</sup>, **Stephanie Berrada**<sup>2</sup>, **Hilton Julius**<sup>3</sup>, **Claire Serrao**<sup>1</sup>, **Dhirisha Naidoo**<sup>1</sup>, **Nthabiseng Koloane**<sup>1</sup>, **Shuabe Rajap**<sup>1</sup>, **Todd Malone**<sup>1</sup>, for the Mpumalanga and KwaZulu-Natal Provincial Research Group

<sup>1</sup>BroadReach Corporation, Cape Town, South Africa, <sup>2</sup>Hospice Palliative Care Association of South Africa, Pretoria, South Africa, <sup>3</sup>CareWorks, Cape Town, South Africa

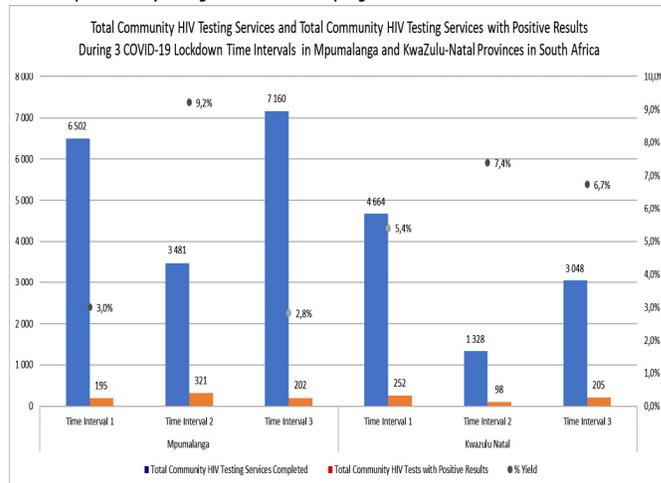
**Background:** BroadReach Healthcare is a PEPFAR district support partner in four districts in two South African Provinces: Mpumalanga (MP) and Kwa-Zulu Natal (KZN). CareWorks and Hospice Palliative Care Association of South Africa (HPCA) are organizations implementing community-based HIV testing services (HTS) under BroadReach Healthcare. During the COVID-19 level-5 lockdown time period, community-based HTS was halted and confined to areas immediately outside of healthcare facilities, and in MP, community-based Lay Counsellors provided HTS in facilities. The aim of this evaluation is to compare HTS rates observed during three 5-week time intervals in 2020: pre-level-5 lockdown (19 February–25 March), during level-5 lockdown (26 March–30 April), and after level-5-lockdown (01 May–06 June).

**Methods:** We conducted an operational evaluation of community and facility data from CareWorks and HPCA: HTS completed, HTS with positive results (HTS\_TST\_POS), and testing yield. Chi-square tests were used to determine statistical significance.

**Results:** Testing decreased in all districts, averaging a 43.1% drop (4,809/11,166) from pre-level-5 lockdown to level-5 lockdown, then rebounded to 91.4% of baseline (10,208/11,166) afterwards (p<0.05). Over the same timescale, HTS\_TST\_POS decreased by only 6.3% (419 from 447) before reverting to 97.1% (407/447) of its pre-level-5 lockdown performance (p<0.05). This was inconsistent across provinces: case finding increased in MP by 64.6% (321 from 195), despite decreased testing, and decreased in KZN by 61.1% (98 from 252). Testing yield was highest during level-5 lockdown in both provinces; averaging 8.7% (419/4,809) compared to 4.0% before (447/11,166) and 4.0% after (407/10,208) level-5 lockdown (p<0.05). MP's testing yield increases far exceeded observed increases in KZN between pre-level-5 lockdown and level-5 lockdown time intervals: 9.2% from 3.0% in MP and 7.4% from 5.4% in KZN (p<0.05).

**Conclusion:** The allocation of community-based Lay Counsellors inside and outside of healthcare facilities during the South African COVID-19 level-5

lockdown assisted with finding people who are HIV-positive, and who are presumably at higher risk of developing severe COVID-19 disease.



**751 A SURVEY-BASED PILOT STUDY TO ASSESS THE EFFECTS OF COVID-19 ISOLATION ON OLDER PLWH**

**Lauren Smith**<sup>1</sup>, **Hannah Walsh**<sup>1</sup>, **Jennifer Chiarella**<sup>1</sup>, **Julian Weiss**<sup>1</sup>, **Serena S. Spudich**<sup>1</sup>, **Shelli F. Farhadian**<sup>1</sup>

<sup>1</sup>Yale University, New Haven, CT, USA

**Background:** Public health emergencies increase stress, anxiety, and fear, and older adults and those with pre-existing conditions may be especially vulnerable. We used a survey-based pilot study to explore the psychosocial impact of COVID-19 on older PLWH and correlate the level of COVID-19 related distress with baseline HIV disease metrics.

**Methods:** Participants were PLWH > age 50 who had previously (2017-2020) enrolled in the HARC HIV biorepository study at Yale. 48 PLWH were contacted and 22 participated in this study, conducted Aug-Sep 2020. An 8-part survey was administered to inquire about COVID-19 exposure, financial distress, medication adherence/medical follow-up, social support, substance use, and mood symptoms (Table 1). Cross-sectional analysis was performed on results at the time of survey administration, and longitudinal analysis was performed to compare anxiety (GAD-7), alcohol/drug use (ASSIST), and depression (CES-D) to baseline values obtained pre-pandemic (median 1.3 years prior).

**Results:** Participant demographics are reported in Table 1. 2 participants reported having been diagnosed with COVID-19, 1 of whom had a known COVID-19 positive contact. 68% of participants were retired and reported no changes to their work due to COVID-19, and most reported moderate (4.1 on scale of 0-7) financial distress. Most reported excellent medication adherence, with 77% reporting no missed doses. 95% stated they felt "very well supported" by their primary HIV care providers, with 18% saying their care was improved during COVID-19. Only 18% felt their care was "somewhat worse." Most participants also scored highly on the social support scale, with an average score of 11 out of 14. There were no significant differences between pre-pandemic and current scores for anxiety, alcohol/drug use, and depression, and there was no correlation between baseline HIV metrics and current level of distress. However, there was an association between COVID-19-associated worsening in GAD-7 score and a history of substance use disorder (p = 0.02).

**Conclusion:** These results suggest that overall, most participants were doing well with excellent medication adherence and no significant changes in scores for anxiety, depression, and substance use, but that older PLWH with a history of substance use disorder had a greater risk for increased anxiety during COVID-19. These findings can help identify groups who may be the most at-risk to experience distress from a second wave of COVID-19 and put support measures in place.

| Survey tools:  |   | Survey type  |   |
|--|---|--|---|
| 1. COVID-19 exposure   |   | Cross-sectional  |   |
| 2. Employment/financial distress                                       |   |  |   |
| 3. Medication adherence  |   |  |   |
| 4. Medical follow-up   |   |  |   |
| 5. Oslo Social Support Scale (OSSS-3)                                  |   | Longitudinal   |   |
| 6. Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) |   |  |   |
| 7. Generalized Anxiety Disorder Assessment (GAD-7)                     |   |  |   |
| 8. Center for Epidemiologic Studies Depression Scale (CES-D)           |   |  |   |
| Demographics   | Medication Adherence                    | Medical Follow-Up  |   |
| Average = 60   | 77.3% - 0 doses                         | 95.5% - "very well supported"  |   |
| Range = 53-69  | 9.1% - 1 dose                           | "How well are you currently being supported by your primary care HIV providers?" |   |
| Median = 58.5  | 4.5% - 2 doses                          | 4.5% - "somewhat well supported"   |   |
| 91% Male   | 4.5% - 6 doses                          |  |   |
| 9% Female  | 4.5% - 10 doses                         |  |   |
| Race   | 68% Non-Hispanic Black/African American | 63.6% - "excellent"  | 9.1% - "significantly improved"   |
|  | 23% Non-Hispanic White                  | 27.3% - "very good"  |   |
|  | 4.5% Hispanic Black/African American    | 9.1% - "fair"  | 9.1% - "somewhat improved"  |
|  | 4.5% Unknown                            |  |   |
| Employment   | 68.2% Retired                           | 77.3% - "always"   |   |
|  | 13.6% Unemployed                        | 13.6% - "almost always"  | "How has the support you receive from your HIV care practice changed due to the COVID-19 outbreak?" |
|  | 13.6% Part-time                         | 4.5% - "usually"   | 63.6% - "no change"   |
|  | 4.6% Full-time                          | 4.5% - "rarely"  | 18.2% - "somewhat worse"  |
| COVID-19 testing   | 14.3% positive (9% of total study)      |  |   |

## 752 HIV AMBULATORY CARE DURING COVID-19 PANDEMIC IN US: VISITS AND VIRAL LOAD TESTING

Ellen M. Tedaldi<sup>1</sup>, Qingjiang Hou<sup>2</sup>, Carl Armon<sup>3</sup>, Frank Palella<sup>3</sup>, Jun Li<sup>4</sup>, Gina Simoncini<sup>1</sup>, Jack Fuhrer<sup>5</sup>, Cynthia Mayer<sup>6</sup>, Kimberly J. Carlson<sup>2</sup>, Kalliope Chagaris<sup>2</sup>, Kate Buchacz<sup>4</sup>

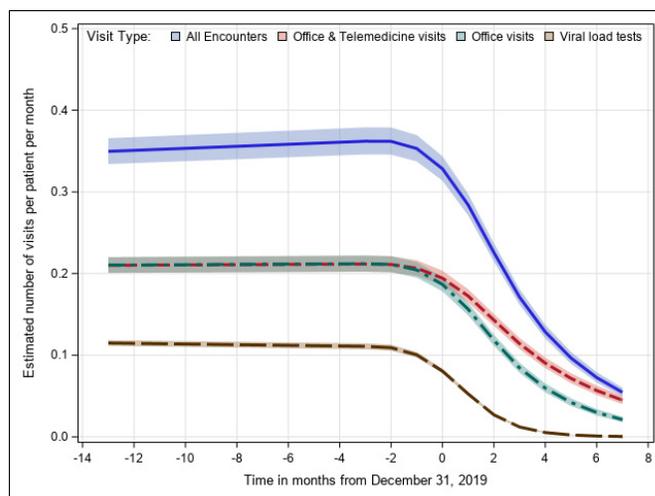
<sup>1</sup>Temple University, Philadelphia, PA, USA, <sup>2</sup>Cerner Corporation, Kansas City, MO, USA, <sup>3</sup>Northwestern University, Chicago, IL, USA, <sup>4</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>5</sup>Stony Brook University, Stony Brook, NY, USA, <sup>6</sup>St Joseph's Comprehensive Research Institute, Tampa, FL, USA

**Background:** COVID-19 pandemic effects on ambulatory care services for persons living with HIV in the United States, including on frequency of office visits and HIV viral load (VL) testing, have not been well described.

**Methods:** We analyzed longitudinal data of active patients (any encounter after January 1, 2020) at 8 HIV Outpatient Study (HOPS) sites. Monthly rates of all-inclusive encounters (office, lab, pharmacy, hospital, telemedicine [TM], phone, other), office and TM (O&T) visits, and HIV VL tests were derived from generalized linear mixed models, using data available from January 2010 to June 2020. We then assessed temporal trends and the adjusted effects of sociodemographic and clinical factors on the rates of O&T visits during the COVID-19 pandemic, in multivariable Poisson regression of data from January to June 2020.

**Results:** Of 1251 active patients, 71% were male, 57% aged  $\geq 50$  years, 36% non-Hispanic white, 42% non-Hispanic black, 19% Hispanic/Latino, and 49% publicly insured. Median CD4 count was 680 cells/mm<sup>3</sup> and 93% had suppressed (<200 copies/mL) VL on last test before January 1, 2020. Patients contributed 10,041 person-years of observation from January 2010 to June 2020. Monthly all-inclusive visit rate (95% Confidence Interval) dropped from 0.33 (0.31, 0.34) in December 2019 to 0.17 (0.16, 0.18) in March 2020, and further declined to 0.07 (0.07, 0.08) in June 2020. The monthly TM rate increased from 0.7% in December 2019 to 2.7% in June 2020 (Figure). In Poisson regression of 2020 data, monthly rate for O&T visits decreased from January to March by 32% and then by another 10% from March to June 2020 (both  $p < 0.001$ ). The decrease was lower with increasing age by 1% (0.5%, 1.5%) per year ( $p < 0.001$ ), and was greater (by 16%) for patients at private clinics than public sites ( $p < 0.05$ ), but did not differ by insurance type, sex, race/ethnicity, or presence of VL suppression on last test (all  $p > 0.20$ ). The increase in TM visits (2%) did not offset the decline in office visits (26%). The HIV VL testing rate fell by 50% in the first 6 months of 2020 among patients who had VL test done in 2019 (Figure).

**Conclusion:** In the HOPS, the rates of office visits and HIV VL tests dropped precipitously after March 2020. The long-term implications for clinical outcomes and HIV viral suppression may not be evident at this time in the COVID-19 pandemic but HIV care sites need strategies to ensure patients maintain engagement in care and HIV laboratory monitoring.



## 753 HITS: A COMMUNITY-RANDOMIZED TRIAL TO INCREASE LINKAGE TO CARE IN RURAL SOUTH AFRICA

Hae-Young Kim<sup>1</sup>, Thulile Mathenjwa<sup>2</sup>, Maryam Shahmanesh<sup>3</sup>, Janet Seeley<sup>4</sup>, Philippa Matthews<sup>5</sup>, Sally Wyke<sup>5</sup>, Nuala McGrath<sup>6</sup>, Oluwafemi Adeagbo<sup>2</sup>, Maxime Inghels<sup>7</sup>, Handurugamage M. Yapa<sup>8</sup>, Thembelihle Zuma<sup>2</sup>, Adrian Dobra<sup>9</sup>, Ann Blanford<sup>3</sup>, Till Bärnighausen<sup>10</sup>, Frank Tanser<sup>2</sup>

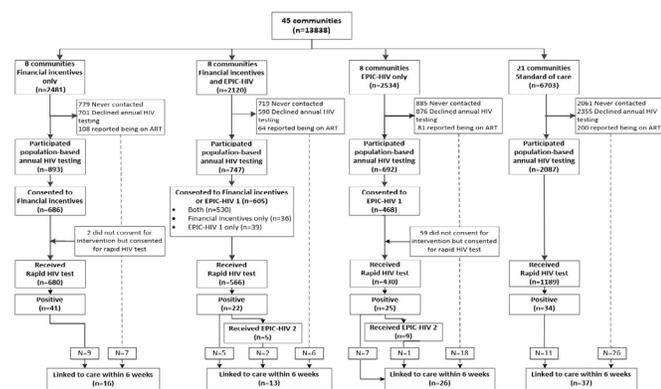
<sup>1</sup>New York University Grossman School of Medicine, New York, NY, USA, <sup>2</sup>Africa Health Research Institute, Mtubatuba, South Africa, <sup>3</sup>University College London, London, UK, <sup>4</sup>London School of Hygiene & Tropical Medicine, London, UK, <sup>5</sup>University of Glasgow, Glasgow, UK, <sup>6</sup>University of Southampton, Southampton, UK, <sup>7</sup>University of Lincoln, Lincoln, UK, <sup>8</sup>University of New South Wales, Sydney, Australia, <sup>9</sup>University of Washington, Seattle, WA, USA, <sup>10</sup>Heidelberg University, Heidelberg, Germany

**Background:** HIV elimination in South Africa requires innovative approaches to ensure men test for HIV and start treatment to reduce onwards transmission. We investigated the effectiveness of intrinsic and extrinsic motivators to increase uptake of HIV testing and linkage to care in a 2x2 factorial cluster randomized controlled trial, "Home-Based Intervention to Test and Start" (HITS), in rural South Africa. Conditional financial incentives significantly increased home-based HIV testing uptake among men. Here, we report the effect of the intervention on linkage to care.

**Methods:** Between February and December 2018, in the uMkhanyakude district of KwaZulu-Natal, we randomly assigned 45 communities to one of four arms: (i) conditional financial incentives for home-based HIV testing and linkage to care within 6 weeks (R50 [\$3] food voucher each); (ii) male-targeted HIV-specific decision-support app based on self-determination theory; (iii) both conditional financial incentives and EPIC-HIV; and (iv) standard of care (SoC). EPIC-HIV was individually offered to men via a tablet at the point of HIV test offer (EPIC-HIV1) or 1 month after home-based HIV testing if individuals who tested positive had not linked to care (EPIC-HIV2). We examined linkage to care (new initiation or re-start of ART after >2 months of care interruption) at local clinics within 6 weeks of a home visit. Intention-to-treat (ITT) analysis was performed using modified Poisson regression with adjustment for clustering of standard errors at the community level.

**Results:** Among all 13,838 men  $\geq 15$  years living in the 45 communities, 20.7% ( $n=2,865$ ) received home-based HIV testing, which resulted in 122 HIV-positive tests including 104 individuals who were newly diagnosed through the trial. The probability of having an HIV-positive test was significantly higher in all intervention arms. A total of 92 individuals, including 35 who received home-based positive tests, initiated ART or resumed care within 6 weeks of a home visit. In the ITT analysis, the probability of linkage to care was significantly higher in the EPIC-HIV only arm (risk ratio [RR]=1.86; 95% CI:1.19–2.92), compared to SoC. There was no increase in linkage to care within 6 weeks in the financial incentives only arm (RR=1.19, 95% CI:0.55–2.54) or the combined arm (RR=1.11, 95% CI:0.56–2.20), compared to SoC.

**Conclusion:** During a single round of interventions to improve linkage to care, a theory-based decision-support intervention increased linkage to care among men.



**Figure 1.** Flow diagram for the HITS cluster-randomized controlled trial and linkage to care within 6 weeks of a home visit. Flow diagram shows individual flow through each stage of the HITS trial by intervention arms. The dashed line indicates linkage to care within 6 weeks among those who were never contacted or declined annual HIV testing. Abbreviation: EPIC, Empowering People through Informed Choices for HIV.

**754 WOMEN ARE LESS LIKELY TO RECEIVE DOLUTEGRAVIR-BASED FIRST-LINE ART IN SOUTH AFRICA**

**Jienchi Dorward<sup>1</sup>, Yuktेशwar Sookraj<sup>2</sup>, Kelly Gate<sup>3</sup>, Thokozani Khubone<sup>2</sup>, Lara Lewis<sup>4</sup>, Christopher C. Butler<sup>1</sup>, Hope Ngobese<sup>2</sup>, Nigal Garrett<sup>4</sup>**  
<sup>1</sup>University of Oxford, Oxford, UK, <sup>2</sup>eThekweni Municipality Health Unit, Durban, South Africa, <sup>3</sup>Bethesda Hospital, Ubombo, South Africa, <sup>4</sup>Centre for the AIDS Programme of Research in South Africa, Durban, South Africa

**Background:** South Africa has the largest ART programme globally and is currently transitioning to WHO recommended dolutegravir (DTG) first-line ART. As there were initial safety concerns for women who conceive while receiving DTG, we compared DTG rollout between sexes.

**Methods:** We analyzed routine data from 59 primary care clinics in KwaZulu-Natal, South Africa, between DTG introduction, in Dec 2019, to Jun 2020. Initially, DTG was prioritised for ART initiations, and women of child-bearing potential were required to sign a South African Health Products Regulatory Authority (SAHPRA) 'acknowledgement of risk' form. In Feb 2020, the SAHPRA form was removed, and people receiving first-line ART were also eligible for switch to DTG. We used Poisson regression models with robust standard errors, and Cox proportional hazards models, to assess the association between sex and the outcomes of 1) initiating, or 2) being switched to, first-line DTG.

**Results:** Of 13,395 adults newly initiated on ART, 8543 (63.8%) were women, median age was 32 years (IQR 26-38) and 6004 (44.8%) were initiated after the SAHPRA form was removed. 4460 (33.3%) initiated DTG and 8928 (66.7%) initiated efavirenz-based regimens. DTG initiation was lower in women (adjusted risk ratio [aRR] 0.76, 95% CI 0.76-0.77), younger people (15-24 years aRR 0.91, 95% CI 0.88-0.93; 24-49 years aRR 0.94, 95% CI 0.92-0.96 vs 50+ years) and those with TB (aRR 0.88, 95% CI 0.85-0.91), and higher in the rural district (aRR 1.20, 95% CI 1.17-1.24) and after the SAHPRA form was removed (aRR 1.28, 95% CI 1.26-1.29). Of 168,952 adults already receiving first-line ART, 115,301 (68.6%) were women, median age was 37 years (IQR 31-44) and median time on ART was 3.89 years (IQR 1.97-6.49). By 30 June 2020, 31,445 (18.6%) had been transitioned to first-line DTG. Switching to DTG was lower in women (adjusted hazard ratio [aHR] 0.42, 95% CI 0.41-0.43), younger people (15-24 years aHR 0.45, 95% CI 0.43-0.48; 24-49 years aHR 0.66, 95% CI 0.64-0.68 vs 50+ years), and in rural clinics (aHR 0.43, 95% CI 0.40-0.46). In sensitivity analyses testing for interactions, the effect of sex was largest in women younger than 50 years old in both the ART initiation (p<0.001) and first-line switching models (p<0.001).

**Conclusion:** In South African clinics, women were less likely to receive DTG than men. Efforts to improve DTG uptake among women should be strengthened, especially as recent evidence suggests lower risks from conceiving on DTG than originally feared.

**Table: Univariable & multivariable analysis of factors associated with being initiated or switched to first-line DTG**

|  | Non-DTG regimen, n (%) | DTG regimen, n (%) | Univariable               | Multivariable             |
|--|------------------------|--------------------|---------------------------|---------------------------|
| <b>Initiation on first-line DTG, n = 13,395, risk ratios</b> |                        |                    |                           |                           |
| Sex  | Male                   | 2077 (42.8)        | -                         | -                         |
|  | Female                 | 6858 (80.3)        | 0.76 (0.75-0.77, p<0.001) | 0.76 (0.76-0.77, p<0.001) |
| Age (years)  | 50+                    | 416 (52.1)         | -                         | -                         |
|  | 25-49                  | 6642 (65.1)        | 0.91 (0.89-0.93, p<0.001) | 0.94 (0.92-0.96, p<0.001) |
|  | 15-24                  | 1877 (78.4)        | 0.82 (0.80-0.84, p<0.001) | 0.91 (0.88-0.93, p<0.001) |
| District   | Urban                  | 8763 (67.3)        | -                         | -                         |
|  | Rural                  | 172 (45.0)         | 1.17 (1.13-1.21, p<0.001) | 1.20 (1.17-1.24, p<0.001) |
| WHO Stage at ART initiation                                  | Stage 1                | 7614 (67.2)        | -                         | -                         |
|  | Stage 2                | 818 (62.3)         | 1.04 (1.02-1.06, p<0.001) | 1.02 (1.00-1.04, p=0.059) |
|  | Stage 3                | 323 (66.6)         | 1.00 (0.97-1.04, p=0.794) | 1.00 (0.96-1.03, p=0.901) |
|  | Stage 4                | 27 (56.2)          | 1.08 (0.98-1.19, p=0.114) | 1.02 (0.94-1.12, p=0.606) |
|  | Not ascertained        | 153 (71.8)         | 0.96 (0.92-1.01, p=0.141) | 0.93 (0.35-0.74, p=0.002) |
| TB at ART initiation   | No TB                  | 8502 (66.4)        | -                         | -                         |
|  | Known TB               | 433 (72.3)         | 0.96 (0.93-0.98, p=0.002) | 0.88 (0.85-0.91, p<0.001) |
| SAHPRA form requirement?                                     | Yes                    | 5067 (84.4)        | -                         | -                         |
|  | No                     | 3868 (52.3)        | 1.28 (1.26-1.29, p<0.001) | 1.28 (1.26-1.29, p<0.001) |
| <b>Switch to first-line DTG, n = 168,952, hazard ratios</b>  |                        |                    |                           |                           |
| Age (years)  | 50+                    | 16523 (72.9)       | -                         | -                         |
|  | 25-49                  | 110298 (82.1)      | 0.63 (0.61-0.65, p<0.001) | 0.66 (0.64-0.68, p<0.001) |
|  | 15-24                  | 10686 (89.6)       | 0.37 (0.34-0.39, p<0.001) | 0.45 (0.43-0.48, p<0.001) |
| District   | eThekweni              | 131012 (81.0)      | -                         | -                         |
|  | uMkhanyakude           | 6495 (90.1)        | 0.44 (0.41-0.47, p<0.001) | 0.43 (0.40-0.46, p<0.001) |
| Sex  | Male                   | 37172 (70.0)       | -                         | -                         |
|  | Female                 | 100335 (86.6)      | 0.40 (0.39-0.41, p<0.001) | 0.42 (0.41-0.43, p<0.001) |

**755 POPULATION IMPACT OF COMMUNITY-BASED ART IN SOUTH AFRICA: A MODELING ANALYSIS**

**Cara Bayer<sup>1</sup>, Maitreyi Sahu<sup>1</sup>, Allen Roberts<sup>1</sup>, Roger Ying<sup>2</sup>, Darcy Rao<sup>1</sup>, Heidi Van Rooyen<sup>3</sup>, Alastair Van Heerden<sup>3</sup>, Thulani Ngubane<sup>3</sup>, Philip Joseph<sup>3</sup>, Ruanne Barnabas<sup>1</sup>**  
<sup>1</sup>University of Washington, Seattle, WA, USA, <sup>2</sup>Yale University, New Haven, CT, USA, <sup>3</sup>Human Sciences Research Council, Pretoria, South Africa

**Background:** In South Africa, a lower proportion of men living with HIV are virally suppressed than women. The Delivery Optimization of Antiretroviral Therapy (DO ART) Study recently demonstrated that community-based delivery of antiretroviral therapy (ART) significantly increased HIV viral suppression compared to standard clinic delivery and eliminated the gender disparity in viral suppression. However, the impact of community-based ART delivery on population-level HIV incidence and mortality is needed.

**Methods:** We parameterized an HIV transmission model with data from the DO ART Study and population surveys to evaluate the impact of community-based ART delivery on HIV in KwaZulu-Natal, South Africa, a province with 27% HIV prevalence. Based on outcomes from the standard of care arm of DO ART, we estimated that 62% of women and 40% of men living with HIV are virally suppressed with clinic-based services. To represent community-based ART delivery, we modeled HIV testing campaigns that linked 90% of persons living with HIV not engaged in care to community-based ART, of whom 73% of women and 72% of men achieved viral suppression (66% suppression overall). We evaluated the 5 and 40 year impact on prevalence, incidence, and mortality of this expanded strategy compared to standard services.

**Results:** Under clinic-based standard of care, the projected annual HIV incidence in 2020 is 2.5% (Range using 25 best-fitting parameter sets: 1.7-3.4%) among women and 1.1% (Range: 0.7-1.7%) among men. Within 5 years, we estimate that community-based ART delivery reduces HIV incidence in women by 32.2% (Range: 29.7-34.4%). By 2060, HIV mortality in women decreases by 37.7% (Range: 34.1-41.3%). Among men, HIV mortality declines by 37.9% (Range: 37.0-39.3%) within 5 years, and HIV incidence decreases by 33.9% (Range: 28.4-42.0%) by 2060. With community-based ART, the ratio of female to male HIV prevalence narrows from 2.9 (Range: 2.3-3.3) in 2020 to 2.1 (Range: 1.7-2.4) in 2060. In total, we estimate that community-based ART delivery will avert 843,421 (Range: 667,114-1,013,236) HIV cases and 683,776 (Range: 548,375-829,802) HIV-associated deaths by 2060.

**Conclusion:** Community-based ART has the potential to quickly and significantly reduce mortality in men and HIV transmission to their female partners, consequently decreasing HIV incidence rates among women. Eliminating disparities in viral suppression is projected to substantially increase population health in generalized epidemic settings with high HIV prevalence.

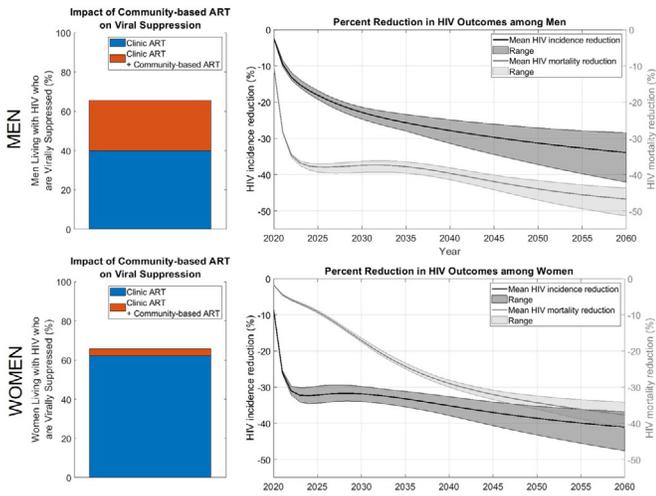


Figure 1: Percent reduction in HIV incidence and HIV mortality afforded by increased viral suppression with community-based ART delivery. Shaded regions represent the range of estimates using the 25 best-fitting model parameter sets.

**756 COACH MPIOLO: A PEER-SUPPORT INTERVENTION TO IMPROVE MEN'S ART LINKAGE & RETENTION**

**Shawn T. Malone**<sup>1</sup>, Mbuzeleni Hlongwa<sup>2</sup>, Kristen Little<sup>2</sup>, Nina Hasen<sup>2</sup>, Melissa Levy<sup>3</sup>, Lucy Clutton<sup>3</sup>, Sunny Sharma<sup>3</sup>, Paris Pitsillides<sup>4</sup>, Chuka Onaga<sup>5</sup>  
<sup>1</sup>Population Services International, Johannesburg, South Africa, <sup>2</sup>Population Services International, Washington, DC, USA, <sup>3</sup>Ipsos Healthcare, London, UK, <sup>4</sup>MatCH, Durban, South Africa, <sup>5</sup>Right to Care, Johannesburg, South Africa

**Background:** Men in South Africa are less likely than women to start and stay on treatment and more likely to die of AIDS-related causes. This project aimed to understand men's barriers to linkage and retention and to co-create and evaluate solutions.

**Methods:** We used a combination of qualitative and quantitative research to analyze individual, social and structural barriers to linkage and retention. We first conducted in-depth interviews with purposively recruited men (n=58), analyzed thematically. We also administered a quantitative survey with randomly selected men (n=2019), analyzed using descriptive and inferential statistics. We then facilitated a series of participatory design workshops with men (n=60) and other stakeholders to identify potential solutions to identified barriers. One intervention—a peer-support model called Coach Mpilo, wherein men living well with HIV coach men still struggling with barriers—was piloted in 3 districts from March–September 2020. We evaluated the pilot using an implementation science approach, focused on assessing effectiveness in improving linkage and retention as well as implementation factors such as acceptability, feasibility, uptake, fidelity, and maintenance, using clinical data as well as interviews, focus groups and surveys.

**Results:** Of the 3848 men enrolled, 1387 were newly diagnosed and 2461 were previously lost-to-follow-up. 3696 men (96%) started or restarted ART during the pilot period, including 1302 (94%) newly diagnosed men and 2394 (97%) men previously LTFU. Of those linked/relinked, 3511 (95%) were retained in care at endline. Retention by cohort (month of enrollment) ranged from 93% to 99%. Retention of men previously LTFU was slightly lower at 94.7% versus 95.5% among newly diagnosed men. 31% of participants were 40–49, 47% were 30–39, 20% were 20–29 and 2% were 15–19. While not the primary aim, the model also appears to have reduced HIV stigma, both internalized and external, with many participants in endline interviews reporting that family and community attitudes about HIV had changed through seeing and interacting with a coach.

**Conclusion:** A peer-support approach, often employed with other target populations, appears to be effective in helping men overcome barriers to HIV treatment and achieving high rates of linkage and early retention, as well as reducing HIV stigma.

|               | Number on treatment by month |     |     |     |     |     |     |
|---------------|------------------------------|-----|-----|-----|-----|-----|-----|
|               | Mar                          | Apr | May | Jun | Jul | Aug | Sep |
| March cohort  | 376                          | 337 | 347 | 351 | 348 | 350 | 349 |
| Retention     |                              | 90% | 92% | 93% | 93% | 93% | 93% |
| April cohort  |                              | 888 | 804 | 816 | 822 | 820 | 825 |
| Retention     |                              | 91% | 92% | 93% | 92% | 93% | 93% |
| May cohort    |                              |     | 996 | 927 | 932 | 937 | 933 |
| Retention     |                              |     | 93% | 94% | 94% | 94% | 94% |
| June cohort   |                              |     |     | 661 | 639 | 642 | 643 |
| Retention     |                              |     |     | 97% | 97% | 97% | 97% |
| July cohort   |                              |     |     |     | 496 | 484 | 484 |
| Retention     |                              |     |     |     | 98% | 98% | 98% |
| August cohort |                              |     |     |     |     | 279 | 277 |
| Retention     |                              |     |     |     |     | 99% | 99% |

**757 COVERAGE OF VIRAL LOAD MONITORING DURING PREGNANCY IN SOUTH AFRICA, NATIONAL SURVEY**

**Selamawit A. Woldesenbet**<sup>1</sup>, Tendesayi Kufa-Chakezha<sup>1</sup>, Samuel Manda<sup>2</sup>, Adrian Puren<sup>1</sup>

<sup>1</sup>National Institute for Communicable Diseases, Johannesburg, South Africa, <sup>2</sup>South African Medical Research Council, Cape Town, South Africa

**Background:** Maternal viral load testing for HIV positive women during pregnancy coupled with appropriate and timely interventions to achieve HIV viral suppression can improve maternal health and reduce the risk of mother-to-child transmission of HIV. Studies assessing viral load monitoring among HIV positive pregnant women in South Africa are limited. This study determined the national coverage of maternal viral load monitoring focusing on viral load testing, documentation of viral load test results, and viral suppression (viral load <50 copies/ml).

**Methods:** Between 1 October and 15 November 2019, a cross-sectional survey was conducted among 15–49 year old pregnant women attending antenatal care in 1 589 nationally representative public health facilities. Data on antiretroviral therapy (ART) status, viral load testing, viral load result documentation, and viral suppression were extracted from medical records. Survey-based logistic regression examined factors associated with coverage of viral load testing. All analyses took into account survey design.

**Results:** Of 8 112 pregnant women eligible for viral load testing (905 women who initiated ART during pregnancy and received ART for at least 3 months, and 7 207 women who initiated ART before pregnancy), 81.7% received a viral load test, of which 94.1% of viral load test results were documented in the medical records (Figure 1). Among those with documented viral load test results, 74.1% were virally suppressed. A lower proportion (73.0%) of women who initiated ART during pregnancy received viral load testing compared to women who initiated ART before pregnancy (82.8%). Viral suppression was low (56.8%) among women who initiated ART during pregnancy. Viral suppression was 76.1% among women who initiated ART before pregnancy. Initiation of ART during pregnancy rather than before pregnancy was associated with a lower likelihood of receiving a viral load test during pregnancy (adjusted odds ratio: 1.6, 95% confidence interval: 1.4–1.8).

**Conclusion:** Most (81.7%) women received viral load testing and results documentation was high (94.1%). The low viral suppression among pregnant women initiating ART during pregnancy highlights the importance of enhanced adherence counselling and the need to fast-track the roll-out of Dolutegravir to enable achievement of more rapid viral suppression. The coverage of viral load testing could be improved further by implementing quality improvement initiatives.

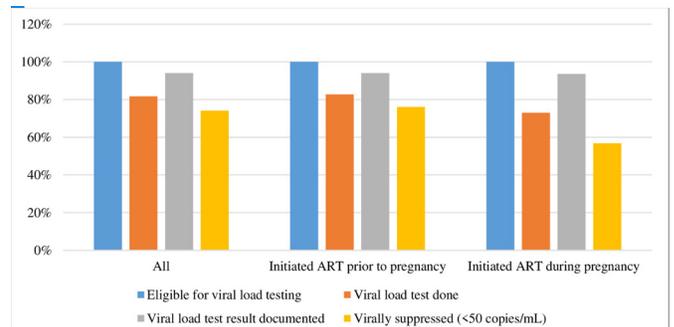


Figure 1: Viral load cascade among pregnant women in the national antenatal sentinel survey, 2019, South Africa

**758 PREDICTORS OF VIRAL LOAD NONSUPPRESSION AT 6 MONTHS OF ART: SHARE STUDY 2015-2017**

Samuel Sendagala<sup>1</sup>, Rose B. Nakityo<sup>1</sup>, Grace Namayanja<sup>1</sup>, Marjorie S. Najjengo<sup>2</sup>, Arthur B. Sekiziyivu<sup>2</sup>, Elizabeth A. Bancroft<sup>3</sup>, Andrew Kambuğu<sup>2</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Kampala, Uganda, <sup>2</sup>Infectious Diseases Institute, Kampala, Uganda, <sup>3</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** Virologic suppression is a core component of the WHO/UNAIDS 90-90-90 strategy of achieving HIV epidemic control by 2020. Uganda rolled out routine viral load (VL) testing in August 2014. This analysis aimed to determine the predictors of VL non-suppression 6 months after ART initiation in a public-sector ART programme in a resource limited setting.

**Methods:** Data from a 2-arm parallel, un-blinded, randomized controlled trial of nurse-initiated and monitored antiretroviral therapy (NIMART) versus clinician-initiated and monitored ART (CIMART) in HIV-infected adults in Uganda from 2015 to 2017 were analyzed. Study participants included HIV-infected, ART-naïve, clinically stable adults initiated on ART at HIV treatment clinics within eight public regional referral hospitals. The primary outcome was viral load non-suppression (VL >1,000 copies/ml) at 6 months on ART. Generalized binomial regression with identity link function was used to determine statistically significant non-inferiority of viral non-suppression of NIMART from the CIMART initiated patients if the 97.5% upper CI of the difference was less than or equal to 6% margin of error. Multivariable logistic regression was used to assess predictors of viral non-suppression. Study site was included as a fixed term in both models to control for potential confounding.

**Results:** Over half of the study cohort of 1,686 were female (55.3%). The overall median age was 33 years (IQR: 28-41). Almost half of the participants (49.9%) were enrolled in NIMART. Median baseline VL was 37,258 copies/ml [IQR: 7,252-118,778], with 87.8% of participants having a baseline viral load > 1,000 copies/ml. The median baseline CD4 count was 343 cells/mm<sup>3</sup> [IQR: 210-433], 23.4% of participants had <200 cells/mm<sup>3</sup> at baseline. Sixty percent (1,007) had a VL test done at 6 months of whom 77 (7.7%) were not virologically suppressed. NIMART was found to be non-inferior to CIMART for VL non suppression at 6 months [Risk Difference=0.0018, 97.5%CI: -0.031-0.035]. At the multivariate level, baseline CD4 cell count <200 copies/mm<sup>3</sup> [aOR=2.4, 95%CI: 1.4-4.2], and age <35 years [aOR=2.3, 95%CI: 1.3-3.9] were statistically significant predictors of viral load non suppression at 6 months.

**Conclusion:** HIV Care from either a nurse or clinician achieved the same 6-month virologic response among HIV patients newly initiated on ART. Patients newly initiating ART who are younger than 35 years and or with CD4 <200 cells/mm<sup>3</sup> may require more treatment support to optimize VL suppression.

**759 COVID-19 SEVERITY AND MORTALITY AMONG HOSPITALIZED PATIENTS IN ZAMBIA**

Peter Minchella<sup>1</sup>, Davies Kampamba<sup>2</sup>, Megumi Itoh<sup>1</sup>, Duncan Chanda<sup>2</sup>, Jonas Hines<sup>1</sup>, Sombo Fwoloshi<sup>2</sup>, Mary A. Boyd<sup>1</sup>, Kotey Nikoi<sup>2</sup>, Lameck Chirwa<sup>2</sup>, Aggrey Mweemba<sup>2</sup>, Suilanji Sivile<sup>2</sup>, Khozya D. Zyambo<sup>2</sup>, Simon Agolory<sup>1</sup>, Lloyd Mulenga<sup>2</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Lusaka, Zambia, <sup>2</sup>Ministry of Health, Lusaka, Zambia

**Background:** Zambia-where HIV prevalence is 11.5% - is experiencing widespread transmission of COVID-19. Studies of clinical outcomes of COVID-19 among HIV-infected individuals have shown mixed results of the impact of HIV status on disease severity or mortality. However, unlike Zambia, most of these studies originated from countries with low prevalence of HIV, with the HIV-infected individuals comprising a small fraction of the overall COVID-19 patient population. We describe the clinical outcomes of patients with SARS-CoV2 infections who were admitted in COVID-19 treatment facilities in Zambia. Specifically, we assessed associations between HIV infection and COVID-19 severity and mortality.

**Methods:** We collected demographic and clinical information from all adult patients admitted with SARS-CoV2 infection across five inpatient facilities in Zambia from July to October 2020. Logistic regression was utilized to examine the association between HIV status and COVID-19 severity, defined as the need for supplemental oxygen at any point during admission; and survival analyses were employed to explore the relationship between HIV status and 28-day mortality. Regression analyses were adjusted for age, sex, and facility.

**Results:** There were 182 cases of severe COVID-19 among 271 enrolled patients. Overall, 66 (24%) patients were HIV-infected, 146 (54%) were male, and 53 (20%) were >60 years. Most HIV-infected patients (87%) were on antiretroviral

therapy (ART) and among those with viral load results, 86% were virally suppressed (<1000 cp/ml). Compared to HIV-uninfected patients, those who were HIV-infected had lower BMI (mean: 26.0 vs. 28.0, p=0.05), and were less likely to be hypertensive (34.8% vs. 47.4%, p=0.01). HIV infection was not a significant predictor of severe disease (adjusted odds ratio: 1.71, 95% CI: 0.88 – 3.46), nor was it associated with 28-day mortality (adjusted hazard ratio: 0.87, 95% CI: 0.39 – 1.94).

**Conclusion:** In this study from a sub-Saharan African (SSA) country with a generalized HIV epidemic, HIV had no statistically significant impact on COVID-19 severity or mortality. Most of the HIV-infected population in this study were virally suppressed and this may indicate that with optimal ART and achievement of HIV viral suppression, the risk of severe disease or mortality from COVID-19 among people living with HIV (PLHIV) can be minimized. Additional studies that assess impact of COVID-19 on PLHIV not on ART are needed, as this group continues to make up a large portion of PLHIV in SSA.

Demographic/clinical characteristics of patients admitted to COVID-19 treatment centers and association with 28-day mortality (N=271)

|   | Unadjusted risk of 28-day COVID-19 mortality |             |         | Adjusted for age, sex, and facility |              |         |
|---|--|-------------|---------|-------------------------------------|--------------|---------|
|   | HR   | 95% CI      | p-value | HR                                  | 95% CI       | p-value |
| Male (ref = female)                                     | 1.7  | 0.86 – 3.2  | 0.133   | 1.90                                | 0.97 – 3.71  | 0.062   |
| Age   |  |             |         |                                     |              |         |
| 15-34 years   | ref  |             |         | ref                                 |              |         |
| 35-49 years   | 1.6  | 0.56 – 4.7  | 0.369   | 1.33                                | 0.45 – 3.92  | 0.600   |
| 50-59 years   | 1.6  | 0.53 – 4.6  | 0.417   | 1.39                                | 0.41 – 4.11  | 0.550   |
| 60+ years   | 3.9  | 1.40 – 10.6 | 0.009   | 3.87                                | 1.39 – 10.80 | 0.001   |
| BMI (ref = <25 kg/m <sup>2</sup> )                      | 0.85   | 0.41 – 1.8  | 0.671   | 0.956                               | 0.44 – 2.06  | 0.91    |
| Preadmission diabetes* (ref = no preadmission diabetes) | 1.4  | 0.66 – 2.9  | 0.39    | 1.19                                | 0.55 – 2.59  | 0.660   |
| Hypertension* (ref = no hypertension)                   | 1.0  | 0.54 – 1.9  | 0.999   | 1.09                                | 0.52 – 2.27  | 0.820   |
| HIV (ref = HIV-uninfected)                              | 0.71   | 0.32 – 1.5  | 0.378   | 0.87                                | 0.39 – 1.94  | 0.740   |

Univariate cox regression and multi variable mixed effects cox regression were used to model the relationship between select demographic/clinical variables and 28-day mortality. Adjusted models included age and sex as fixed effects and a random effects term for facility. Abbreviations: HR = Hazard Ratio, CI = confidence interval, BMI = body mass index, ref = reference category

\*Preadmission diabetes defined based on self-reported status at treatment center admission

\*Hypertension defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg at treatment center admission

**760 HIV CARE OUTCOMES AMONG ASIANS WITH DIAGNOSED HIV INFECTION: UNITED STATES, 2018**

Sonia Singh<sup>1</sup>, Xueyuan Dong<sup>2</sup>, William Adih<sup>1</sup>, Nicole Crepaz<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA, <sup>2</sup>ICF International, Atlanta, GA, USA

**Background:** From 2010–2016, the Asian population in the U.S. grew approximately 17%. From 2010–2017, the rate of diagnosis of HIV infection for Asians increased and varied by age, while rates of deaths remained stable. Assessing HIV care outcomes among Asians is critical for targeted prevention efforts and to reduce transmission of HIV infection.

**Methods:** Data from 42 National HIV Surveillance System sites with complete laboratory reporting to CDC through December 2019 were used to determine the numbers of Asians with HIV diagnosis, the percentages linked to care within one month after diagnosis, retained in care and virally suppressed in 2018 by sex, age and transmission category.

**Results:** Among 786 Asians with HIV infection diagnosed in 2018, 206 (26.2%) had infection classified as stage 3 (AIDS). The highest percentage of persons with HIV infection diagnosed at stage 3 (AIDS) were those 13-34 years for males and 35-54 years for females. In 2018, 662 (84.2%) were linked to care within one month after diagnosis. Males (78.4%) and females (76.5%) ≥55 years had the lowest linkage to care. Among 13,096 Asians living with diagnosed HIV infection at year-end 2017, 9,819 (75.0%) received any care, 7,681 (58.7%) were retained in care and 9,121 (69.6%) were virally suppressed in 2018. Females had lower receipt of care and retention in care than males. The lowest retention in care for males (58.8%) and females (55.2%) was among those aged 35-54 years. The lowest retention in care among those whose infection was attributed to injection drug use (IDU) was males ≥55 years (42.6%) and females 13-34 years (50.3%). The lowest retention in care among those whose infection was attributed to heterosexual contact was males ≥55 years (56.2%) and females 35-54 years (55.2%). The lowest viral suppression for males (66.8%) and females (65.2%) was among those aged ≥55 years, as well as for all transmission

categories except for infection attributed to heterosexual contact among females. The lowest viral suppression was among males (47.7%) and females (56.0%) whose infection was attributed to IDU.

**Conclusion:** HIV care outcomes among Asians were below national goals. Age and risk group appropriate strategies for Asians are needed. To address late diagnosis, HIV testing should be targeted to males 13–34 years and females 35–54 years. Increased linkage to care, receipt of care and achievement of viral suppression is needed for those  $\geq 55$  years. Improvements in retention in care for those 35–54 years are also needed.

## 761 RETENTION AND VIRAL LOAD SUPPRESSION AMONG ADULTS LIVING WITH HIV ON ART IN LESOTHO

**Yingfeng Wu**<sup>1</sup>, Claude M. Muvunyi<sup>1</sup>, Frederic Koen<sup>2</sup>, Felix Ndagije<sup>3</sup>, Julia Frieze<sup>1</sup>, Tsetso Motosoane<sup>3</sup>, Mosilinyane Letsie<sup>2</sup>, Johannes Mengistu<sup>4</sup>, Joshua R. DeVos<sup>5</sup>, Joy C. Chang<sup>5</sup>, Elaine J. Abrams<sup>1</sup>, Juliana Da Silva<sup>5</sup>, Elliot Raizes<sup>5</sup>

<sup>1</sup>ICAP at Columbia University, New York, NY, USA, <sup>2</sup>ICAP at Columbia University, Maseru, Lesotho, <sup>3</sup>Ministry of Health, Maseru, Lesotho, <sup>4</sup>Centers for Disease Control and Prevention, Maseru, Lesotho, <sup>5</sup>Centers for Disease Control and Prevention, Atlanta, GA, USA

**Background:** Lesotho has one of the highest HIV prevalence worldwide. A national cross-sectional survey was conducted to evaluate rates of retention on antiretroviral therapy (ART) and viral load (VL) suppression among adults ( $\geq 18$  years old) living with HIV (ALHIV) on ART as part of a study on HIV drug resistance (HIVDR) during 2018–2019.

**Methods:** A stratified two stage (clinics/patients) probability proportional to size (PPS) sampling design was used to achieve representative samples from three targeted ALHIV population. Sample 1 includes ALHIV who initiated ART 15–27 months prior to the survey. Sample 2 and 3 includes current ALHIV who have been on ART for 9–15 months and for  $\geq 48$  months respectively. Sample 1 was used to evaluate retention rates (proportion of patients who had a clinic visit within 12+/-3 months after ART initiation excluding documented out-transfers or known dead) by reviewing patient charts. Laboratory tests for HIV VL were conducted for ALHIV in sample 2 and 3 to evaluate VL suppression rate (proportion of patients with VL < 1000 copies/mL). Proportions and 95% confidence intervals are used to estimate prevalence. Chi-square test and logistic regression models were used to investigate correlates of retention and/or VL suppression. Sampling weights were applied to and PPS design was accounted for all analysis.

**Results:** Among 501 ALHIV in sample 1, 60% were female, median age was 37 years (IQR: 29–46 years). The overall retention rate was 75.3% (95% CI: 67.5–83.1%). While district differences in retention rates were observed ( $p < 0.001$ ), retention rates did not differ by sex or age groups. VL suppression rates among ALHIV on ART for 12 months ( $n = 385$ ) and  $\geq 48$ -mo ( $n = 490$ ) cohorts were high at 93.4% (95%CI: 90.2–95.6%) and 92.1% (95%CI: 88.5–94.6%), respectively. While VL suppression did not differ by sex, younger age groups had lower VL suppression at 12 months ( $p < 0.01$ ) and 48 months ( $p < 0.01$ ). In the 12-month cohort, older age groups (adjusted odds ratios [AOR]: 95% CI): 25–44 years: 1.4 [1.1, 1.6],  $\geq 45$  yrs: 25.8 (16.4, 40.5), 18–24 years as reference) and ALHIV with no prior ART exposure (AOR(95%CI): 18.2 [11.3–29.3]) had higher VL suppression rates in logistic regression model. Few ALHIV (2 in sample 2 and 3 in sample 3) were on 2nd line ART regimen and all had VLS.

**Conclusion:** While VLS rates among ALHIV retained in care are high, retention rate was sub-optimal. Younger age groups and ALHIV with prior ART exposure require tailored intervention to improve VLS.

Table. Rates of retention and viral load suppression among adults living with HIV on antiretroviral therapy in Lesotho, 2018–2019 survey

|                    | Retention at month 12, n=501 |                          | Viral load suppression rate among 12 months cohort, n=385 |                   | Viral loads suppression rate among 248 months cohort, n=490 |                   |
|--------------------|------------------------------|--------------------------|---|-------------------|---|-------------------|
|                    | Sample, col %                | Retention, row %, 95% CI | Sample, col %   | VLS, row %, 95%CI | Sample, col %   | VLS, row %, 95%CI |
| Total              | 100                          | 75.3, 67.5–87.1          | 100   | 93.4, 90.2–95.6   | 100   | 92.1, 88.5–94.6   |
| Sex                |                              |                          |   |                   |   |                   |
| Female             | 60.0                         | 75.9, 70.5–81.3          | 66.4  | 93.6, 86.1–96.6   | 77.5  | 91.9, 88.1–94.6   |
| Male               | 40.0                         | 74.4, 67.6–81.3          | 33.7  | 92.4, 89.1–96.3   | 22.5  | 92.7, 85.1–96.5   |
| Age (years)        |                              |                          |   |                   |   |                   |
| 18–24              | 9.7                          | 58.6, 41.6–75.6          | 15.4  | 89.6, 74.4–96.2   | 3.9   | 87.2, 45.1–98.2   |
| 25–44              | 61.4                         | 77.6, 72.5–82.7          | 64.1  | 92.9, 87.7–96.0   | 49.0  | 90.5, 85.7–93.8   |
| $\geq 45$          | 28.9                         | 76.0, 68.3–83.8          | 15.6  | 97.7, 83.6–99.7   | 47.2  | 94.2, 90.2–96.6   |
| Prior ARV exposure |                              |                          |   |                   |   |                   |
| Yes                | No data                      |                          | 1.2   | 63.9, 0–100       | No data   |                   |
| No                 | No data                      |                          | 98.8  | 93.9, 89.6–96.5   | No data   |                   |

## 762 IMPACT OF IMMEDIATE ART FOR PATIENTS WITH KNOWN HIV EXPERIENCING A GAP IN HIV CARE

**Catherine Pearson**<sup>1</sup>, Katerina Christopoulos<sup>1</sup>, Pierre-Cedric Crouch<sup>1</sup>, Noelle LeTourneau<sup>1</sup>, Manami Diaz Tsuzuki<sup>1</sup>, Patricia Defechereux<sup>1</sup>, Jason Bena<sup>2</sup>, Kelvin Moore<sup>2</sup>, Coleton Schmitto<sup>3</sup>, Elise S. Mara<sup>3</sup>, Ling Hsu<sup>3</sup>, Susan Scheer<sup>3</sup>, Robert Grant<sup>1</sup>, Janessa Broussard<sup>2</sup>

<sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>San Francisco AIDS Foundation, San Francisco, CA, USA, <sup>3</sup>San Francisco Department of Public Health, San Francisco, CA, USA

**Background:** Immediate antiretroviral therapy (ART) at HIV diagnosis is endorsed by DHHS guidelines. Less is known about the impact of immediate ART for individuals with known HIV who are either not in care or facing a lapse in care.

**Methods:** Since 2016, San Francisco AIDS Foundation (SFAF)/Magnet, a nurse-led, community-based sexual health and wellness clinic without on-site primary care, has provided immediate interim ART, support services, and care linkage to individuals with known HIV who are not in care or facing a lapse in care. Data on services needed/rendered, ART, and viral load (VL) were abstracted from the medical record and supplemented by pre and post-visit VL data from the San Francisco Department of Public Health. We calculated the proportion of individuals who achieved viral suppression (VS) as well as those found to maintain VS on first VL obtained after their SFAF encounter; we considered those with missing follow up VL as all suppressed or all unsuppressed in a sensitivity analysis (SA).

**Results:** Between October 2016 and March 2020, 260 individuals with known HIV presented to SFAF needing services to support HIV management. Individuals had median age of 34 years and were 97% cis-men, 65% MSM, 33% Hispanic, 8% Black. At presentation, 189 (73%) were on ART, 61 (23%) were ART experienced but not taking ART, 10 (4%) were ART naïve. The most common reasons for presenting were loss of insurance 58%, relocation 37%, STD services 17%, or a problem with long-term HIV provider 11%. The most common services provided were ART prescription 92%, lab services to maintain benefits 66%, linkage support 63%, and medical or pharmacy benefits support 60%. Of 239 individuals requesting ART prescription, 99.6% received one: 93% same-day and 97% within 7 days. Of 143 individuals without evidence of VS at baseline, 75% (SA 60%–80%) were suppressed on first follow up VL. Of 117 individuals with VS at baseline, 94% (SA 80–95%) sustained VS. Of ART naïve individuals, 90% accepted ART initiation, 89% of whom subsequently demonstrated VS.

**Conclusion:** A nurse-led sexual health center without on-site primary care can successfully prevent viral load rebound in individuals facing care lapses and achieve suppression in those never or no longer in care. Given the majority of forward HIV transmission is from those with known HIV who are not virologically suppressed, expanding the immediate ART paradigm to include those previously diagnosed is an important tool for improving both individual and population health.

## 763 DIFFERENCES IN SEXUAL BEHAVIORS BEFORE AND AFTER UNIVERSAL TEST AND TREAT IN UGANDA

**Brendah Nansereko**<sup>1</sup>, Fred Nalugoda<sup>2</sup>, Alex Daama<sup>2</sup>, Fred Makumbi<sup>1</sup>, Edward N. Kankaka<sup>2</sup>, Joseph Kagaayi<sup>2</sup>, Gertrude F. Nakigozi<sup>2</sup>, David Sserwadda<sup>2</sup>, Nelson Sewankambo<sup>2</sup>, Michelle Adler<sup>3</sup>, Tom Lutalo<sup>2</sup>, M. Kate Grabowski<sup>4</sup>, Godfrey Kigozi<sup>2</sup>

<sup>1</sup>Makerere University, Kampala, Uganda, <sup>2</sup>Rakai Health Sciences Program, Kalisizo, Uganda, <sup>3</sup>Division of Global HIV & TB, US Centers for Disease Control and Prevention, Kampala, Uganda, <sup>4</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

**Background:** Universal Test and Treat (UTT) with antiretroviral therapy (ART) reduces HIV morbidity and mortality rates and the risk of transmission. The 2015 World Health Organization ART initiation guidelines called for implementation of universal ART as part of Universal Test and Treat programs (UTT). However, there has been concern that increased use of ART could alter HIV risk perception, and lead to risk compensation, which could potentiate the continued spread of the epidemic especially in HIV hotspot areas like the fishing communities. We assessed the impact of universal test and treat on sexual behaviors in the Rakai Community Cohort Study (RCCS).

**Methods:** We used RCCS data from 2011–2018 for consenting participants aged 15–49 years. The main exposure period was prior to UTT initiation 2011/2013 (R015) versus after UTT from 2014–2018. Risky sexual behaviors were inconsistent condom use with any sexual partner in the past 12 months, multiple sexual partners, alcohol use before sexual intercourse and unknown

HIV status of sexual partner. We stratified analysis by fishing communities and non-fishing communities. Frequency distributions were used to estimate prevalence of risk behaviors and chi square statistic to assess significant differences before and after UTT initiation periods. A mixed-effects logistic model was fitted to estimate the association of UTT on selected risky sexual behaviors. We adjusted for age in years, gender, occupation, highest education level, marital status, and community type.

**Results:** A total of 14,193 participants were enrolled in this study. Of these, 25% (3556) were from fishing communities. Inconsistent condom use was the most of selected sexual risk behaviors, both before and after initiation of UTT (90.0% and 91.7% respectively) and was not significantly different post-UTT ( $P=0.327$ ). After UTT, there was 21.0% decrease in the proportion of participants who lacked knowledge about their partners' HIV status (from 54.9% before UTT to 33.9% after UTT;  $P<0.001$ ). While prevalence of inconsistent condom use was lower in the fishing communities compared to the non-fishing communities before and after UTT.

**Conclusion:** We found no evidence of risk compensation among sexual behaviors in the era of UTT implementation, though prevalence of the selected sexual behaviors remains consistently high in fishing compared to non-fishing communities. UTT has resulted in increasing proportion of persons knowing the HIV status of their sexual partners.

**764 APPLYING MACHINE LEARNING TO ROUTINE HIV DATA: PREDICTING MISSED CLINIC VISITS**

Mhairi Maskew<sup>1</sup>, Lucien De Voux<sup>2</sup>, Kieran Sharpey-Schaefer<sup>2</sup>, Thomas Crompton<sup>3</sup>, Jacqui Miot<sup>1</sup>, Sydney Rosen<sup>4</sup>

<sup>1</sup>University of the Witwatersrand, Johannesburg, South Africa, <sup>2</sup>Palindome Data, Cape Town, South Africa, <sup>3</sup>Right to Care, Centurion, South Africa, <sup>4</sup>Boston University, Boston, MA, USA

**Background:** To optimize South Africa's HIV response and reach targets of 95% tested, 95% treated, and 95% virally suppressed, numbers initiating and successfully remaining on antiretroviral therapy (ART) must increase. While much effort and resources have been focused on tracing those lost to follow up and returning them to care, little prior work has successfully addressed identifying those most at risk of poor treatment outcomes while they are still engaged in care.

**Methods:** We applied machine learning and modelling algorithms to routinely-collected ART patient data from the SLATE I and SLATE II trials which evaluated same-day ART initiation in 2017-18. Our primary outcome was the probability of a patient's attending the next scheduled clinic visit. Three classification algorithms were tested: logistical regression, random forest and AdaBoost classifier. Demographic, clinical, socioeconomic, care-seeking behavioural (visit patterns), and laboratory data points were investigated as potential predictor variables. Predictions were scored for accuracy against known outcomes in the source dataset.

**Results:** Data from 916 patients who initiated ART were analyzed in 7 models using multiple combinations of input features and classification algorithms. The best model achieved 90% specificity and 69% accuracy and an area under the curve of 0.68 for attendance at next scheduled visit, suggesting that the model correctly anticipated whether a scheduled visit would be attended for 2 out of 3 patients. Prior patient behavior and treatment history were important in predicting visit attendance, while demographic and socioeconomic characteristics were useful in creating patient profiles to stratify groups (Table 1) into risk profiles. Compared to punctual attenders with social support, a patient who is late to previous appointments was 1.69 times more likely to miss a scheduled visit, while an employed patient aged 18-29 with a scheduled visit near payday was 1.21 times more likely to miss the next visit.

**Conclusion:** If facilities could identify patients at higher risk of loss to care while the patient is still active, micro-targeted interventions could be implemented more efficiently and pro-actively, rather than only after a patient is lost. Predictive models may allow providers to combine existing medical record data on prior behavior and treatment history with a simple demographic and socioeconomic questionnaire to assess individual risk and offer personalized, differentiated care.

Table 1: Risk of missing scheduled clinic visit stratified by patient profile group

| Patient Profile Group                   | n visits | Pop% | LTFU% | Risk difference (RD) | Relative risk (RR) | 95% CI      |
|---|----------|------|-------|----------------------|--------------------|-------------|
| SUPER_GREEN*                            | 2,739    | 32%  | 10.7% | Reference            | 1.00               | -           |
| EMPLOYED YOUTH AT PAYDAY <sup>1</sup>   | 347      | 4%   | 13.0% | 2.3%                 | 1.21               | 0.91 - 1.63 |
| PRIOR TEST AND PROMPT <sup>2</sup>      | 2,013    | 24%  | 13.1% | 2.4%                 | 1.22               | 1.03 - 1.45 |
| LONE RANGER <sup>3</sup>                | 1,739    | 20%  | 14.5% | 3.8%                 | 1.35               | 1.15 - 1.58 |
| UNEXPECTED AND UNSUPPORTED <sup>4</sup> | 964      | 11%  | 14.3% | 3.6%                 | 1.35               | 1.12 - 1.64 |
| DISILLUSIONED DISCLOSER <sup>5</sup>    | 1,394    | 16%  | 15.4% | 4.7%                 | 1.43               | 1.21 - 1.69 |
| LIVE CLOSE ALWAYS LATE <sup>6</sup>     | 1,138    | 13%  | 17.3% | 6.6%                 | 1.61               | 1.37 - 1.91 |
| PREPARED AND LATE <sup>7</sup>          | 551      | 6%   | 18.1% | 7.4%                 | 1.69               | 1.37 - 2.08 |

**Definitions:**  
 \*Super green (reference group) = punctual visit attendance, doesn't live alone  
<sup>1</sup>Employed youth at payday = Age 18-29, identify as employed AND next visit scheduled <7 days from payday  
<sup>2</sup>Prior test and Prompt = Has a history of HIV testing (before testing positive) AND regularly prompt for visits  
<sup>3</sup>Lone ranger = Lives alone or with 1 other person AND lives more than 20 mins away  
<sup>4</sup>Unexpected and Unsupported = was not planning to test for HIV today AND lives alone/with 1 other person  
<sup>5</sup>Disillusioned Disclosers = Identifies as having HIV info, has disclosed, lives alone or with 1 other person  
<sup>6</sup>Live close Always late = lives within 20 minutes but is also regularly late for appointments  
<sup>7</sup>Prepared and Late = Identifies as prepared to start ART today, has tested before but is late to appointments

**765 VALIDATING A RETENTION-IN-CARE METRIC TO INFORM EFFORTS FOR PREVENTING HIV DEATH**

David B. Hanna<sup>1</sup>, Rachael Lazar<sup>2</sup>, Lindsay Zielinski<sup>2</sup>, Perminder Khosa<sup>2</sup>, Mindy S. Ginsberg<sup>1</sup>, Denis Nash<sup>3</sup>, Kathryn Anastos<sup>4</sup>, Uriel R. Felsen<sup>4</sup>, Sarah L. Braunstein<sup>2</sup>  
<sup>1</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>2</sup>New York City Department of Health and Mental Hygiene, Long Island City, NY, USA, <sup>3</sup>City University of New York, New York, NY, USA, <sup>4</sup>Montefiore Medical Center, Bronx, NY, USA

**Background:** Despite improvements in survival for people with HIV (PWH), nearly 500 deaths are attributed to HIV (28% of all deaths among PWH) in New York City (NYC) yearly. The HIV Mortality Reduction Continuum of Care (HMRC) leverages public health surveillance data and identifies missed opportunities for intervention for these potentially preventable deaths. Our goal was to validate retention in care measured using the HMRC with outpatient visit records of PWH who died of HIV despite receiving care.

**Methods:** We linked data from the NYC HIV Surveillance Registry with the ERC-CFAR Clinical Cohort Database, which contains health records from the Montefiore Health System (MHS), Bronx, NY. Based on local and national vital statistics data, we identified PWH who died in 2016 or 2017 and had sought care at MHS in the previous year. HIV deaths were defined by ICD-10 codes B20-B24. We assessed whether PWH had met definitions of "retention in HIV care" prior to death (2 encounters 90+ days apart within a 1-year "intervention period") based on either HIV laboratory tests (CD4, viral load) reported to surveillance, or HIV outpatient visits in the ERC-CFAR database as the gold standard. We compared retention between PWH who died and those who survived during matched, rolling intervention periods.

**Results:** 402 PWH received care at MHS and died in 2016 or 2017 (median age 56, 37% female, 51% Black, 45% Latino/Hispanic). Among 126 who died due to HIV (31%), retention in care during the intervention period was 40% via surveillance and 33% via HIV outpatient visits (kappa=0.52, moderate agreement). In contrast, among 7,294 PWH who survived during the same period, retention was 62% and 65% respectively (kappa=0.77). Compared with PWH who died due to HIV and were not retained in care (N=75), PWH who died despite being retained (N=51) were more likely to be Latino/Hispanic (59% vs 32%) and less likely to be Black (37% vs 63%,  $p=0.01$ ), and more likely to have evidence of ART prescription (98% vs 51%,  $p<0.001$ ) and undetectable viremia (63% vs 25%,  $p<0.001$ ); CD4 counts were low (median 170 vs 126 cells/uL,  $p=0.58$ ).

**Conclusion:** Among patients receiving HIV care, HIV-related mortality remains substantial. In the absence of outpatient records, surveillance data are reasonable to assess care patterns of those dying of HIV. The HMRC can identify populations who may benefit from interventions to improve retention and those whose HIV-related deaths, despite retention, may inform other interventions along the care continuum.

## 766 ECONOMIC EVALUATION OF DIFFERENTIATED SERVICE DELIVERY OF HIV TREATMENT IN ZIMBABWE

Brooke Nichols<sup>1</sup>, Mariet Benade<sup>1</sup>, Salome Kuchukhidze<sup>1</sup>, Kudakwashe Takarinda<sup>2</sup>, Nicoletta Mabhena-Ngorima<sup>2</sup>, Ashraf Grimwood<sup>3</sup>, Sydney Rosen<sup>1</sup>, Geoffrey Fatti<sup>3</sup>

<sup>1</sup>Boston University, Boston, MA, USA, <sup>2</sup>Ministry of Health and Child Care, Harare, Zimbabwe, <sup>3</sup>Kheth'Impilo AIDS Free Living, Cape Town, South Africa

**Background:** Zimbabwe has >1.4 million people living with HIV, of whom 85% are on antiretroviral treatment (ART), but the country has not yet achieved the UNAIDS 95-95-95 targets, and further expansion of its treatment program will require more efficient use of existing resources. One promising strategy for reducing resource utilization, and thus cost, per patient treated is multi-month dispensing of medications. We evaluated the costs to providers of community-based, multi-month ART delivery models in Zimbabwe.

**Methods:** We used resource and outcome data from a cluster-randomised non-inferiority trial of different models of differentiated service delivery models, targeted to patients stable on ART. The trial compared retention in care at 12 months in care for 3-month facility-based care (standard of care) with that for 3- and 6-month community ART refill groups (CARGs), which dispensed medications for 3- and 6-month intervals at a time, respectively. Using local unit costs, we estimated the annual cost of providing HIV care and treatment per patient from the provider (health system) perspective 12 months after entry into each study arm. Costs are reported in 2018 USD.

**Results:** In the trial, retention at 12 months was 91.0% in the 3-month facility visit arm (SOC), 93.3% in the 3-month CARG arm, and 93.6% in the 6-month CARG arm. The total average annual costs of HIV treatment per patient were \$183 (standard deviation \$32), \$190 (\$32), and \$179 (\$35) in each of the three arms, respectively. The annual cost per patient was dominated by medications (87% in 3-month facility-based care, 83% in 3-month CARG; 92% in 6-month CARG), followed by facility visits (8%, 7%, 5%, respectively) and viral load (5%, 5%, 2%, respectively). If those in the 6-month CARG arm received a similar number of viral loads on average as in the other two arms, the cost-savings of the 6-month CARG arm disappear.

**Conclusion:** While both the 3- and 6-month CARG arms were more effective at retaining patients in care, they had similar costs from the provider perspective as 3-month facility-based care. Costs to the patients should be evaluated in future work, given that lower patient costs can support long-term adherence. Given the cost-neutrality of the CARG models and improved patient outcomes, these models should be prioritized for further scale-up.

|  | Conventional care<br>(3-monthly Facility)<br>n=1916 | 3-month CAGs<br>n=1334    | 6-month<br>community<br>distribution<br>n=1545 |
|--|---|---------------------------|--|
| <b>Resource utilization</b>  |   |                           |  |
| Facility visits (Mean [SD])  | 3.23 (0.890)  | 2.88 (0.931)              | 1.83 (0.527)                                   |
| DSD interactions (Mean [SD])   | 0   | 4.49 (2.81)               | 1.71 (1.26)                                    |
| Viral load (Mean [SD])   | 0.675 (0.585)                                       | 0.723 (0.634)             | 0.192 (0.452)                                  |
| ART months dispensed (Mean [SD])   | 11.4 (1.96)   | 11.4 (1.81)               | 11.9 (2.32)                                    |
| <b>Annual provider costs*</b>  |   |                           |  |
| Facility visits  | \$14.92 (\$4.11)                                    | \$13.32 (\$4.30)          | \$8.47 (\$2.43)                                |
| DSD interactions   | -   | \$8.44 (\$5.28)           | \$3.22 (\$2.37)                                |
| VL   | \$9.73 (\$8.44)                                     | \$10.42 (9.14)            | \$2.77 (\$6.52)                                |
| ART  | \$158.05 (\$27.03)                                  | \$158.04 (\$25.04)        | \$164.95 (\$32.03)                             |
| <b>Total cost (Provider only)</b>  | <b>\$182.70 (\$31.51)</b>                           | <b>\$190.22 (\$31.72)</b> | <b>\$179.41 (\$34.84)</b>                      |
| <b>Annual provider cost per person retained<br/>12 months post model entry</b> | <b>\$188.12 (\$20.67)</b>                           | <b>\$194.38 (\$24.21)</b> | <b>\$182.09 (\$32.49)</b>                      |

\*In 2018 USD

## 767 PATIENT COSTS IN A DIFFERENTIATED SERVICE DELIVERY INTERVENTION IN NORTHWEST TANZANIA

Nwanneka Okere<sup>1</sup>, Lucia Corball<sup>1</sup>, Sabine Hermans<sup>1</sup>, Denise Naniche<sup>2</sup>, Tobias Rinke de Wit<sup>1</sup>, Gabriela Gomez<sup>2</sup>

<sup>1</sup>Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands,

<sup>2</sup>Global Barcelona Institute for Global Health, Hospital Clinic, Barcelona, Spain,

<sup>3</sup>London School of Hygiene & Tropical Medicine, London, UK

**Background:** Placing all clients with a positive diagnosis for HIV on antiretroviral therapy (ART) has cost implications both for patients and health systems, which could in turn affect feasibility, sustainability, and uptake of new services. Patient-incurred costs are recognized barriers to healthcare access. Differentiated service delivery (DSD) models in general and community-based care in particular, show promise for reducing these costs. We aimed to assess patient-incurred costs of a community-based DSD intervention (clubs) compared to clinic-based care in the Shinyanga region, Tanzania.

**Methods:** Cross-sectional survey among stable ART patients (n=390, clinic-based; n=251, club-based care). For each group, we collected socio-demographic, income, and expenditure data. We estimated patient-incurred costs - direct and indirect costs. Direct costs included out-of-pocket expenditures. Indirect costs included income loss due to time spent during transport, accessing services, and off work during illness. Cost drivers were assessed in multivariate regression models.

**Results:** Overall, costs were significantly higher among clinic participants. Costs (USD) per year for clinic vs club were: 11.7 vs 4.17 (p<0.001) for direct costs, 20.2 vs 7.71 (p<0.001) for indirect costs and 31.8 vs 11.9 (p<0.001) for total costs. Time spent accessing care and time spent in illness (hours/year) were 38.3 vs 13.8 (p<0.001) and 16.0 vs 6.69 (p<0.001), respectively. The main cost drivers included transportation (clinic vs club: 67.7% vs 44.1%) for direct costs, and income loss due to time spent accessing care (clinic vs club: 60.4% vs 56.7%) for indirect costs. Factors associated with higher total costs among patients attending clinic services were higher education level (coefficient [95% confidence interval]) 13.0 [0.8, 25.3]), formal employment (30.9 [11.4, 50.5]) and higher income (43.8 [35.4, 52.2]); among those attending the clubs only higher income (9.02 [4.12, 13.9]) was significant. The percentage of households classified as having had catastrophic expenditures in the last year was low but significantly higher among clinic participants (10.8% vs 5.18%, p=0.014).

**Conclusion:** Costs incurred by patients accessing DSD in the community are significantly lower compared to those accessing standard clinic-based care. DSD models provide promising benefits which could improve access and could potentially catalyze the attainment of global targets especially in resource limited settings.



## 768 CHANGES IN HIV DIFFERENTIATED CARE UTILIZATION DURING THE COVID-19 PANDEMIC IN ZAMBIA

Youngji Jo<sup>1</sup>, Sydney Rosen<sup>1</sup>, Amy Huber<sup>2</sup>, Muya Mwansa<sup>3</sup>, Mpende Mwenechanya<sup>3</sup>, Priscilla Lumano-Mulenga<sup>3</sup>, Bevis Phiri<sup>4</sup>, Hilda Shakwele<sup>4</sup>, Prudence Haimbe<sup>4</sup>, Brooke Nichols<sup>1</sup>

<sup>1</sup>Boston University, Boston, MA, USA, <sup>2</sup>Health Economics and Epidemiology Research Office, Johannesburg, South Africa, <sup>3</sup>Ministry of Health, Lusaka, Zambia, <sup>4</sup>Clinton Health Access Initiative, Lusaka, Zambia

**Background:** Differentiated service delivery (DSD) models aim to lessen the burden of HIV treatment on patients and providers in part by reducing requirements for facility visits and extending dispensing intervals. With the advent of the COVID-19 pandemic, minimizing patient contact with healthcare facilities and other patients, while maintaining treatment continuity and avoiding loss to care, has become more urgent, resulting in efforts to increase DSD. In March, the Zambian Ministry of Health urgently promoted the 3- and 6- multi-months dispensing for patients on antiretroviral treatment (ART). We assessed the extent to which DSD coverage and ART dispensing intervals have changed during the COVID-19 pandemic in Zambia.

**Methods:** We used patient data from SmartCare, Zambia's electronic medical record system, for 737 health facilities, representing about 3/4 of all ART patients nationally, to compare the numbers and proportional distributions of patients enrolled in DSD models and the average duration of drug dispensing

between February 15 2020, and October 30 2020, 8 months after the first recorded COVID-19 case in Zambia on March 18, 2020.

**Results:** As expected, participation increased for all DSD models. The number of patients presently enrolled in a DSD model increased by 60% between February and October, from 134,652 (18% coverage) to 215,947 (29% coverage), though remaining below one third of all patients. Home ART delivery saw the greatest percent increase in utilization (240%), while community adherence groups experienced the smallest change (18%), potentially a reflection of efforts to discourage group models due to COVID-19 transmission risk. Although 6-month dispensing is Zambia's national policy for stable patients, the proportion of patients receiving 6-month supplies fell from 57% to 49%, while the proportions of patients receiving a 1, 2 or 3-month supplies rose. The shortening of dispensing intervals is primarily due to patients switching temporarily back from Tenofovir Lamivudine Dolutegravir (TLD) to Tenofovir lamivudine Efavirenz (TLE) to mitigate threats of TLD global supply chain.

**Conclusion:** The months of the COVID-19 pandemic showed increased participation in DSD models for stable ART patients in Zambia but shorter dispensing intervals. Efforts to eliminate obstacles to longer dispensing intervals should be prioritized to achieve the expected benefits of DSD models and minimize COVID-19 risk.

Table. Numbers and proportional distributions of patients enrolled in differentiated service delivery models in Zambia

| Indicator  | As of February 15 2020 |                                       |                                 | As of October 30 2020 |                                       |                                 | % increase in coverage |
|--|------------------------|---------------------------------------|---------------------------------|-----------------------|---------------------------------------|---------------------------------|------------------------|
|  | n                      | % of total patients on ART (coverage) | % of all patients in DSD models | n                     | % of total patients on ART (coverage) | % of all patients in DSD models |                        |
| <b>Model of care</b>   |                        |                                       |                                 |                       |                                       |                                 |                        |
| Multi-month dispensing 3 months                                  | 20,521                 | 3%                                    | 15%                             | 42,198                | 6%                                    | 20%                             | 106%                   |
| Multi-month dispensing 4-6 months                                | 47,677                 | 6%                                    | 35%                             | 66,290                | 9%                                    | 31%                             | 39%                    |
| Fast track + 0-2 month dispensing                                | 10,474                 | 1%                                    | 8%                              | 21,777                | 3%                                    | 10%                             | 108%                   |
| Fast track + 3-month dispensing                                  | 11,712                 | 2%                                    | 9%                              | 19,705                | 3%                                    | 9%                              | 68%                    |
| Fast track + 4-6 month dispensing                                | 24,360                 | 3%                                    | 18%                             | 31,266                | 4%                                    | 14%                             | 28%                    |
| Community adherence group  | 8,437                  | 1%                                    | 6%                              | 9,989                 | 1%                                    | 5%                              | 18%                    |
| Home ART delivery  | 875                    | 0%                                    | 1%                              | 2,978                 | 0%                                    | 1%                              | 240%                   |
| Other model*   | 10,596                 | 1%                                    | 8%                              | 21,744                | 3%                                    | 10%                             | 105%                   |
| <b>Total</b>   | <b>134,652</b>         | <b>18%</b>                            | <b>100%</b>                     | <b>215,947</b>        | <b>29%</b>                            | <b>100%</b>                     | <b>60%</b>             |
| <b>Months of ARV medications dispensed at most recent pickup</b> |                        |                                       |                                 |                       |                                       |                                 |                        |
| 1 month  | 8,691                  |                                       | 6%                              | 17,412                |                                       | 8%                              | 100%                   |
| 2 months   | 5,653                  |                                       | 4%                              | 11,005                |                                       | 5%                              | 95%                    |
| 3-4 months   | 43,012                 |                                       | 32%                             | 79,650                |                                       | 38%                             | 85%                    |
| 5-6 months   | 76,758                 |                                       | 57%                             | 102,211               |                                       | 49%                             | 33%                    |
| <b>Total</b>   | <b>134,114</b>         |                                       | <b>100%</b>                     | <b>210,278</b>        |                                       | <b>100%</b>                     | <b>57%</b>             |

\*Other models include after/before hours, community pharmacy, health post, scholar, rural/urban adherence groups, mobile ART distribution, weekend clinic.

**769 PREDICTORS OF CHOOSING COMMUNITY-BASED ANTIRETROVIRAL THERAPY PICK-UP IN SOUTH AFRICA**

**Ingrid V. Bassett<sup>1</sup>**, Joyce Yan<sup>1</sup>, Sabina Govere<sup>2</sup>, Anele R. Khumalo<sup>2</sup>, Nompumelele Ngobese<sup>2</sup>, Zinhle M. Shazi<sup>2</sup>, Mpilonhle Nzuza<sup>2</sup>, Bridget A. Bunda<sup>1</sup>, Nafisa J. Wara<sup>1</sup>, Ashley Stuckwisch<sup>1</sup>, Danielle Zions<sup>1</sup>, Hilary Thulare<sup>2</sup>, Laura M. Bogart<sup>3</sup>, Robert A. Parker<sup>1</sup>

<sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>AIDS Healthcare Foundation, Durban, South Africa, <sup>3</sup>RAND Corporation, Santa Monica, CA, USA

**Background:** South Africa's government-led Central Chronic Medicine Dispensing and Distribution (CCMDD) Program allows people living with HIV the choice of collecting antiretroviral therapy (ART) at community pick-up points (PUPs) to increase convenience and decongest clinics. To better understand how people use CCMDD, we evaluated factors associated with choosing a community vs. clinic-based PUP.

**Methods:** We collected baseline data on adults (≥18y) who met CCMDD clinical eligibility criteria (not pregnant, on ART for ≥1y, and virologically suppressed) as part of an observational cohort in 7 public clinics in Umlazi, KwaZulu-Natal. In addition to age and gender, we identified predictors of selecting a community PUP and fit a multivariable logistic regression model that included distance to clinic, self-identified barriers to care (service delivery, financial, personal health perception, logistical, and structural), self-efficacy, HIV treatment beliefs, HIV stigma, HIV-related discrimination, and perceived benefits and challenges of enrolling in CCMDD.

**Results:** Among 1520 participants, 67% were female, with median age 36y (IQR 30-44). Choosing a community PUP was associated with younger age (aOR 1.16 per 10y decrease, 95% CI 1.03-1.31, p=0.01), living 10-30km from clinic (aOR 2.26, 95% CI 1.43-3.57, p<0.001), no self-identified barriers to care (aOR 1.43, 95% CI 1.09-1.86, p=0.009), scoring the maximum self-efficacy score (aOR

1.89, 95% CI 1.39-2.59, p<0.001), and reporting any HIV stigma (aOR 1.71, 95% CI 1.32-2.21, p<0.001). Additional predictors included more convenient PUP location (aOR 1.92, 95% CI 1.49-2.46, p<0.001) or hours (aOR 6.06, 95% CI 4.39-8.36, p<0.001) as perceived benefits of CCMDD, and lack of in-clinic follow-up after a missed collection date as a perceived challenge of CCMDD (aOR 3.02, 95% CI 1.59-5.74, p<0.001). Perceiving shorter PUP queues as a benefit of CCMDD was negatively associated with choosing a community PUP (aOR 0.70, 95% CI 0.53-0.93, p=0.012).

**Conclusion:** Selecting a community PUP was associated with younger age and systemic and structural factors of living with HIV (living farther from clinic, no self-identified barriers to care, high self-efficacy, and reporting any HIV stigma) as well as perceptions of CCMDD (convenient PUP locations and hours, challenging in-clinic follow-up), but negatively associated with shorter PUP queues. Strategies to facilitate community PUP selection are needed to maximize the impact of CCMDD in decongesting clinics.

**770 C2C: DIFFERENTIATED CARE INCREASES HIV CARE AFTER PRISON RELEASE IN SOUTH AFRICA**

**Christopher Hoffmann<sup>1</sup>**, Jill Owczarzak<sup>2</sup>, Stefan Baral<sup>2</sup>, Colleen Hanrahan<sup>2</sup>, Tonderai Mabuto<sup>3</sup>

<sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Johns Hopkins University School of Public Health, Baltimore, MD, USA, <sup>3</sup>Aurum Institute, Johannesburg, South Africa

**Background:** Globally a large proportion of people with HIV (PWH) pass through correctional facilities. During incarceration, PWH often achieve an undetectable viral load. Post release, retention in care and on ART is suboptimal, with estimated 34% retention in South Africa. We built upon formative work among reentrants in South Africa and the experience from the United States to develop and test in a randomized trial a multi-level intervention to increase linkage to and retention in HIV care during community reentry in South Africa.

**Methods:** Our intervention was built on the differentiated care concept of community adherence clubs with group meetings. Groups met every two weeks for 6 months for two hours with facilitated interaction by a peer (reentrant living with HIV) and a social worker and included peer bonding, an interactive curriculum, ART provision every two months, and referrals to services not able to be provided through this group. We refer to this intervention as a transitional community adherence club (TCAC). We enrolled and randomized participants 2:1 into the TCAC or care as usual (CAU) (a referral letter from the correctional facility at release). We had follow-up visits with all participants post-release at 1 week and 1, 3, and 6 months. We compared linkage within 90 days of release by arm.

**Results:** We enrolled and randomized 175 incarcerated individuals (116 in TCAC and 59 in CAU); 95% were men, the median age was 33 years, the median duration of incarceration was 10 months, and 32% reported opioid use. Among those with either participant or family contact 41 (23%) were reported to be living on the streets, 19 (11%) were re-incarcerated, 3 (2%) had died, and 86 (49%) reported that they were in care within 90 days. Among TCAC arm participants, 67 (58%) were in care compared to 19 (32%) of CAU (chi square p=0.001).

**Conclusion:** We adapted an existing differentiated care model to successfully increase retention in care during community reentry in South Africa. This is the only intervention reported on care retention during reentry in Africa and one of the few globally to demonstrate success. We hypothesize that the use of peer support and a multilevel intervention contributed to the success. Differentiated care models may have an important role for a variety of populations who are underserved by traditional HIV care models, including community reentrants.

**771 TRANSMISSION IMPACT OF PrEP UPTAKE IN URBAN CENTERS IN BRAZIL: A MODELING STUDY**

**Paula M. Luz<sup>1</sup>**, Vijeta Deshpande<sup>2</sup>, Pooyan Kazemian<sup>3</sup>, Justine Scott<sup>2</sup>, Fatma Shebl<sup>3</sup>, Cristina Pimenta<sup>4</sup>, Gerson Fernando M. Pereira<sup>4</sup>, Claudio Struchiner<sup>2</sup>, Beatriz Grinsztejn<sup>1</sup>, Valdilea Veloso<sup>1</sup>, Kenneth Freedberg<sup>2</sup>, David Paltiel<sup>6</sup>

<sup>1</sup>Oswaldo Cruz Foundation - Fiocruz, Rio de Janeiro, Brazil, <sup>2</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>3</sup>Case Western Reserve University, Cleveland, OH, USA, <sup>4</sup>Ministry of Health, Brasilia, Brazil, <sup>5</sup>Fundação Getúlio Vargas, Rio de Janeiro, Brazil, <sup>6</sup>Yale University, New Haven, CT, USA

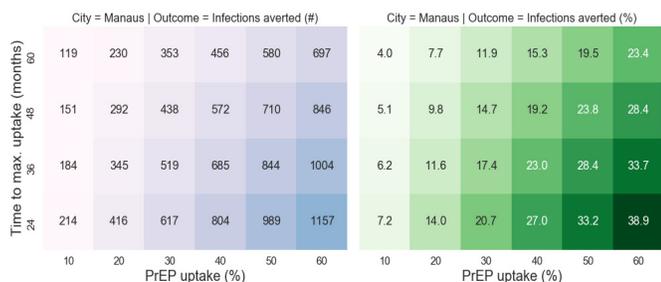
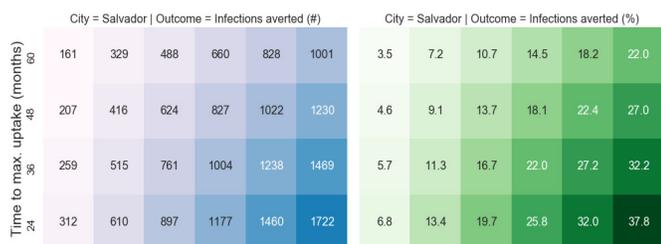
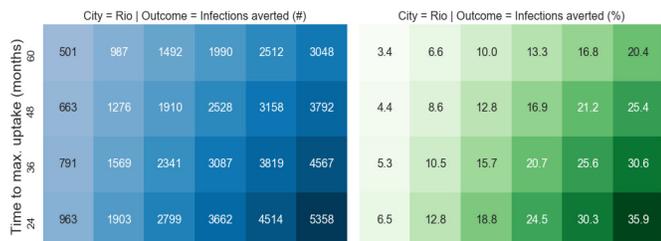
**Background:** Gay, bisexual, and other men who have sex with men (GBM) in Brazil remain disproportionately affected by HIV despite the availability of prevention and treatment. We sought to estimate the clinical benefits of

increasing the uptake of publicly funded, daily, oral tenofovir/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP).

**Methods:** We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model to assess the impact of increasing PrEP uptake to different levels (range 10–60%) across various timelines (within 1–4 years) in a cohort of adult (≥18 years) GBM without HIV. We used local studies, national data, and the international literature to represent the HIV epidemic in three Brazilian cities: Rio de Janeiro (Southeast), Salvador (Northeast), and Manaus (North). Age-stratified HIV incidence rates were highest in Rio de Janeiro (4.3/100 person-year (PY), 2.5/100PY in Salvador and 1.4/100PY in Manaus); PrEP efficacy was 96%, and adherence was 74%. Outcomes included HIV infections, with and without PrEP, over 5 and 10 years. In sensitivity analyses, we examined how results varied with changes in adherence to PrEP (range 50–85%), drop-out rates (range 0–25%/year), and age at initiation of PrEP (21–33 years). We also estimated the PrEP uptake level needed to reach a 75% incidence reduction in 5 years.

**Results:** We found that a PrEP intervention achieving 10% uptake among GBM within 60 months could avert 501 infections in Rio de Janeiro (Salvador: 161, Manaus: 119) by 5 years. An intervention achieving 60% uptake among GBM within 24 months would avert ~10-times as many infections (35.9% incidence reduction in Rio de Janeiro, 37.8% in Salvador, and 38.9% in Manaus). In sensitivity analyses, increasing PrEP adherence to 85% would increase the number of averted infections by 14%; decreasing adherence to 50% would reduce averted infections by 31%. If the cohort mean age decreased to 21 years at PrEP start, then averted infections increased by 42%, while including drop-out rate decreased the transmission impact of PrEP. To reach 75% incidence reduction in 5 years, a PrEP intervention would need to achieve 80% uptake among GBM over 36 months.

**Conclusion:** Increased oral PrEP uptake in Brazil would substantially decrease HIV transmission over the next 5 to 10 years. PrEP uptake would need to be extremely high to achieve a proposed target of 75% incidence reduction within 5 years.



772 **MODELING PrEP IMPACT AND COST-EFFECTIVENESS BASED ON THE ImPrEP DEMONSTRATION PROJECT**

**Annick Borquez**<sup>1</sup>, Kelika A. Konda<sup>2</sup>, Oliver A. Elorreaga<sup>2</sup>, Ximena Gutierrez<sup>2</sup>, Juan V. Guanira<sup>3</sup>, Sonia Flores<sup>2</sup>, Gino M. Calvo<sup>2</sup>, Carlos F. Caceres<sup>2</sup>

<sup>1</sup>University of California San Diego, San Diego, CA, USA, <sup>2</sup>Universidad Peruana Cayetano Heredia, Lima, Peru, <sup>3</sup>INMENZA, Lima, Peru

**Background:** While PrEP efficacy among men who have sex with men (MSM) and transgender women (TW) has been demonstrated, a key step to inform its national scale up in low and middle income countries is to evaluate its impact and cost effectiveness under real world conditions. From 2018 to 2020, the ImPrEP demonstration project enrolled 1954 MSM and 275 TW in public sexual health clinics and an NGO in six cities in Peru, providing rich data to inform an HIV epidemic and economic model of PrEP impact.

**Methods:** We used data from the ImPrEP project to perform a micro-costing analysis of adding PrEP to services provided by public sexual health clinics. This included ongoing costs of ARV drugs, laboratory tests, transport and personnel, as well as start-up costs related to equipment and infrastructure. We informed our dynamic model which explicitly represents transmission among 4 main groups: gay-identified MSM, bisexual/heterosexual-identified MSM, male sex workers (MSW) and TW with ImPrEP data on PrEP uptake, retention and adherence by group to estimate impact and cost-effectiveness of PrEP scale-up on reducing HIV incidence between 2022–2030.

**Results:** The cost of one year of PrEP provision was estimated at USD \$1,065, with a third of these costs attributable to ARV drugs (\$75/person/year) and laboratory testing. Of the participants, 59% identified as gay, 14% identified as heterosexual/bisexual, 14% were MSW and 13% were TW. Assuming observed patterns of PrEP uptake, retention and adherence by group between 2022–2030, scaling up PrEP to 20% of the MSM/TW population, could avert 26% (95%CI: 22%–32%) of new HIV infections. Impact would be highest among TW with 46% (95%CI: 34%–60%) of new infections averted. The cost per DALY averted would be of \$6,186 (95%CI: \$3,192–\$11,387). This is within the WHO threshold of 1 GDP/capita (\$6,941) and the Peru specific threshold estimated by Woods (\$7747), but above that estimated by Ochalek (\$1300), which is more stringent as it is based on the correlation between changes in health expenditure and in mortality/morbidity in Peru.

**Conclusion:** PrEP implementation by the Ministry of Health (MoH) in Peru at a feasible coverage of 20% would significantly reduce HIV incidence among MSM and TW and would be cost-effective under most thresholds. However, enhancing retention and adherence would improve efficiency. Additionally, some costs would benefit from MoH economies of scale. Importantly, such PrEP program would reduce HIV disparities among TW.

773 **HIV RISK-PREDICTION MODEL USING ELECTRONIC HEALTH RECORD DATA IN A SOUTHERN COHORT**

**Charles Burns**<sup>1</sup>, Leland Pung<sup>1</sup>, Daniel Witt<sup>1</sup>, Michael Gao<sup>1</sup>, Mark Sendak<sup>1</sup>, Douglas Krakower<sup>2</sup>, Julia Marcus<sup>2</sup>, Nwora Lance Okeke<sup>1</sup>, Meredith E. Clement<sup>3</sup>

<sup>1</sup>Duke University, Durham, NC, USA, <sup>2</sup>Harvard Medical School, Boston, MA, USA, <sup>3</sup>Louisiana State University, New Orleans, LA, USA

**Background:** HIV pre-exposure prophylaxis (PrEP) is underutilized in the southern US, a region that accounts for half of new incident HIV cases nationwide. Uptake may be limited by difficulties in identifying candidates for PrEP. Electronic health record (EHR)-based models can identify men at highest risk for HIV infection who would most benefit; however, these models have performed poorly in women and have not been developed in Southern cohorts.

**Methods:** We developed a model to predict incident HIV diagnosis among patients within the Duke Health System (DUHS). Patients were aged ≥18 and seen at DUHS between Oct. 2014 and Aug. 2018. Patients with an initial positive Ag/Ab or RNA test were identified, then two independent physicians performed chart adjudication to confirm incident HIV diagnosis during the study period. Clinical and demographic EHR data were used to obtain 41 feature vectors as potential predictors of incident HIV diagnosis based on published models and clinical experience. The risk prediction model was developed using an ensemble learning algorithm, Extreme Gradient Boosting (XGBoost), and validated with a 70–30 train/test split. Shapley Additive explanations (SHAP) were calculated for individual variables for visualized interpretation. Model performance was assessed, overall and among women, by area under the receiver operator characteristic curve (AUC) and average precision scores (APS).

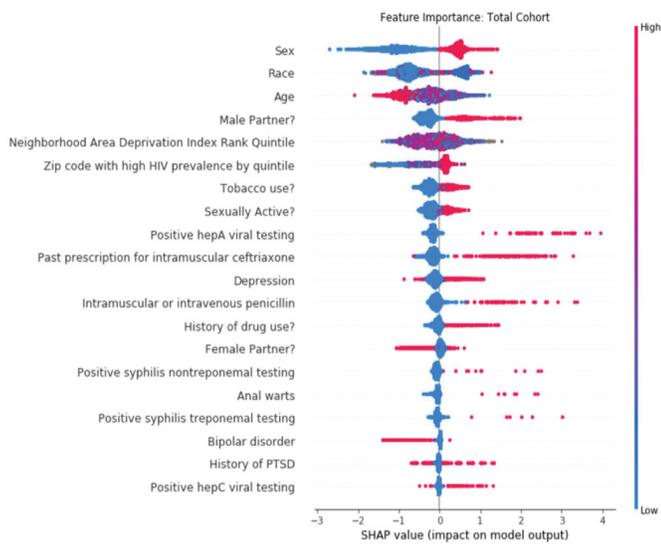
**Results:** Of 1.618 million unique DUHS patients during the study period, we identified 368 patients with incident HIV diagnosis, of whom 93 were female.

For the total patient cohort, our model had an AUC of 0.96 with an APS of 0.45. For the female-only cohort, the AUC was 0.95 with an APS of 0.27. We determined the most predictive variables of HIV risk based on their individual SHAP values (Fig. 1). Globally, the most predictive variables for both cohorts were race, age, and zip code. The most impactful predictors for the total cohort were hepatitis A (reactive IgM), receipt of IM ceftriaxone, and receipt of IM penicillin, and for the female-only cohort were hepatitis A, buprenorphine or methadone usage, and history of domestic or sexual abuse.

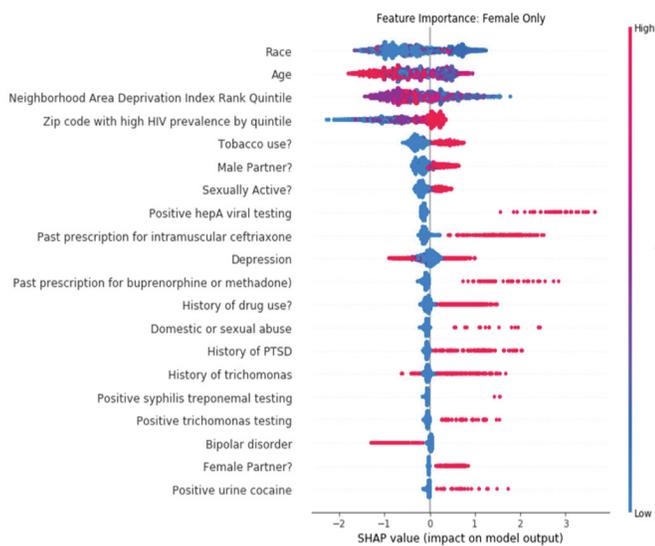
**Conclusion:** Our models had high AUCs and acceptable precision scores in general and for women, reflecting their ability to identify individuals at increased risk for incident HIV diagnosis in a Southern health system. This is the first EHR-prediction model with acceptable performance for women and holds promise to optimize PrEP implementation in the South.

Figure 1.

### Shapley Additive Explanation (SHAP) Values of Individual Electronic Health Record Variables



A) Total Cohort



B) Female Patients Only

### 774 INVESTMENT IN A KEY POPULATION HIV PROGRAM IN NIGERIA: A COST-EFFECTIVENESS ANALYSIS

**Moses Katbi**<sup>1</sup>, **Adefisayo Adedoyin**<sup>2</sup>, **Helina Meri**<sup>1</sup>, **Kent Klindera**<sup>3</sup>, **Adeoye Adegboye**<sup>1</sup>, **Abdulmalik Abubakar**<sup>1</sup>, **Amalachukwu Ukaere**<sup>4</sup>, **Abdulsamad Salihu**<sup>4</sup>, **Wole Fajemisin**<sup>4</sup>, **Segun K. Fatoye**<sup>4</sup>, **Rachel Goldstein**<sup>1</sup>

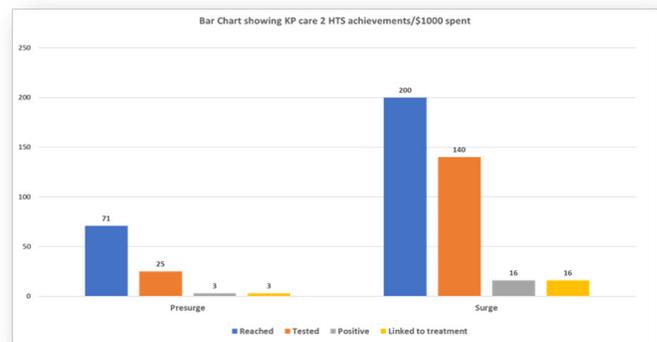
<sup>1</sup>United States Agency for International Development, Abuja, Nigeria, <sup>2</sup>Independent Consultant, Abuja, Nigeria, <sup>3</sup>United States Agency for International Development, Washington, DC, USA, <sup>4</sup>Society for Family Health, Abuja, Nigeria

**Background:** Key populations (KPs) - including men who have sex with men (MSM), female sex workers (FSW), people who inject drugs (PWID), and transgender people (TG) account for 32% of new HIV infections in Nigeria. Investing in KP programs is critical to achieving HIV epidemic control. We increased the HIV case-finding targets for KPs in two geographic areas while increasing investment in human and financial resources. This study looked at the cost effectiveness of increasing investment for the KP program.

**Methods:** A multi-centric retrospective study covering a six-month period divided into pre-surge (October 2019-February 2020) and surge (March-April 2020). We implemented routine HIV services during the pre-surge, while in the surge period, human and financial resources were increased in line with an increased program target. Number of peer navigators was increased from 66 (pre-surge) to 226 (surge) and budget from \$47,614 (pre-surge) to \$112,504 (surge). Target for HIV positive clients was also increased from 187 (pre-surge) to 1,914 (surge). We conducted a Cost effectiveness analysis (CEA) based on clients reached, tested, positives identified and linked to treatment. Chi square and Spearman's rank order correlation was used to determine the relationship between every \$1,000 spent per period and the outcome variables.

**Results:** Pre-surge, \$47,614 was spent with 66 peer navigators engaged, reaching 3,380 KPs at a cost per target (CPT) of \$14, testing 1,200 KPs (CPT=\$40), and identified 138 new positive clients (CPT=\$345) with 126 linked to treatment (CPT=\$375) giving a linkage rate of 91%. For surge, \$112,504 was spent with 226 peer navigators engaged reaching 23,060 KPs (CPT=\$5), tested 15,554 (CPT=\$7), and identified 1,811 new positive KPs (CPT=\$63), with 1,757 linked to treatment (CPT=\$64) giving a linkage rate of 97%. CEA shows that for every \$1000 spent at pre-surge, 71 KPs were reached, 25 tested with 3 positive cases identified. With surge, for every \$1000 spent, 200 clients were reached, 140 tested with 16 new positive identified. Chi square test of independence showed the relationship between project period and achievement/\$1000 spent was statistically significant ( $\chi^2 = 7.768$ ,  $df = 2$ ,  $p = 0.021$ ). Spearman rank order correlation shows a positive correlation between project period and achievement/\$1000 spent ( $r_s = 0.129$ ,  $p = 0.006$ ).

**Conclusion:** Increasing investment for KPs is a valuable approach towards achieving HIV epidemic control among a group disproportionately infected with HIV.



### 775 PROJECTED IMPACT OF TARGETED PrEP AND VIRAL SUPPRESSION AMONG MSM IN 4 US CITIES

**Melissa Schnure**<sup>1</sup>, **Parastu Kasaie**<sup>1</sup>, **David Dowdy**<sup>1</sup>, **Maunank Shah**<sup>2</sup>, **Anthony T. Fojo**<sup>2</sup>

<sup>1</sup>The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>2</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Background:** The announcement of the United States' Ending the HIV Epidemic (EHE) initiative in 2019 articulated a comprehensive strategy to end HIV in high-burden jurisdictions across the country. However, the localized nature of

the HIV epidemic in the US suggests that decisions regarding specific priority interventions and key populations must be made at the local level.

**Methods:** We applied Johns Hopkins Epidemiological and Economic Model (JHEEM), a dynamic, compartmental model of HIV epidemic in US, to evaluate the relative benefits of increased pre-exposure prophylaxis (PrEP) coverage versus improved viral suppression in young (age <35) men who have sex with men (MSM) versus all MSM. We selected four metropolitan statistical areas (MSAs) for comparison: Los Angeles, New York City, Atlanta, and Baltimore. In each MSA, we compared scenarios corresponding to improved PrEP coverage (proportion of individuals at risk for HIV infection who are prescribed and adherent to PrEP and tested for HIV every three months) and improved viral suppression at three levels, assuming scale-up from 2021-2022, with continuation from 2022-2030. Our primary outcome was the MSA-wide reduction in HIV incidence by 2030, evaluated as the mean across 200 independent model simulations.

**Results:** Across the four MSAs, scaling up PrEP among young MSM yielded large reductions in incidence, while the marginal impact of expanding PrEP interventions to all MSM was modest. The possible benefit of improved suppression, on the other hand, was maximized by scale-up among all MSM more broadly. For example, in Los Angeles, 25% PrEP coverage among young MSM (versus all MSM) reduced ten-year HIV incidence by a projected 38% (versus 49%), whereas increasing suppression to 85% provided a 26% (versus 51%) reduction. Overall, an optimistic strategy of focused PrEP among young MSM (25% coverage) plus broad increases in suppression among all MSM (85% suppression) could lead to a 58-70% reduction in HIV incidence by 2030, while an aspirational strategy of 50% PrEP coverage among young MSM combined with 90% suppression among all MSM was nearly sufficient to meet EHE targets (74-83% reduction in HIV incidence by 2030).

**Conclusion:** The impact of improved PrEP coverage and viral suppression varies substantially at the local level, but model projections suggest that a strategy targeting PrEP to young MSM while improving suppression levels among MSM in care more broadly could be effective.

**Figure:** Ten-year reduction in HIV incidence across four Metropolitan Statistical Areas. Values represent the percent reduction in incidence by 2030 (averaged across 200 simulations) across the entire MSA population, given select PrEP or suppression interventions in young MSM versus all MSM.

|                                       | No intervention | Young MSM (<35) |     |     |             |     |     | All MSM |     |     |             |     |     |
|---------------------------------------|-----------------|-----------------|-----|-----|-------------|-----|-----|---------|-----|-----|-------------|-----|-----|
|                                       |                 | PrEP            |     |     | Suppression |     |     | PrEP    |     |     | Suppression |     |     |
|                                       |                 | 10%             | 25% | 50% | 80%         | 85% | 90% | 10%     | 25% | 50% | 80%         | 85% | 90% |
| Los Angeles-Long Beach-Anaheim, CA    | 3%              | 20%             | 36% | 56% | 20%         | 26% | 31% | 26%     | 49% | 71% | 39%         | 51% | 63% |
| New York-Newark-Jersey City, NY-NJ-PA | 16%             | 28%             | 42% | 56% | 25%         | 32% | 38% | 32%     | 50% | 67% | 28%         | 41% | 56% |
| Atlanta-Sandy Springs-Alpharetta, GA  | 6%              | 17%             | 32% | 51% | 28%         | 33% | 37% | 20%     | 39% | 62% | 46%         | 55% | 64% |
| Baltimore-Columbia-Towson, MD         | 19%             | 31%             | 44% | 57% | 35%         | 39% | 43% | 35%     | 52% | 69% | 41%         | 50% | 59% |



**Results:** We recruited 1179 participants in Montreal, 517 in Toronto and 753 in Vancouver. The RDS-adjusted HIV prevalence was 14.2% (95% CI:11.1-17.2) in Montreal; 22.1% (95% CI:12.4-31.8) in Toronto, and 20.4% (95% CI:14.5- 26.3) in Vancouver ( $p < 0.001$ ). Of participants with confirmed HIV infection, 3.3% were previously undiagnosed in Montreal, 3.2% undiagnosed in Toronto and 0.2% in Vancouver ( $p = 0.154$ ). In Montreal, 87.6% of GBM living with HIV were receiving antiretroviral therapy (ART) and 10.6% had an unsuppressed VL; in Toronto, 82.6% were receiving ART and 4.0% were unsuppressed; in Vancouver, 88.5% were receiving ART and 2.6% were unsuppressed ( $p < 0.001$  for receiving ART and 0.009, for unsuppressed VL). Multivariable modelling demonstrated that participants in Vancouver (adjusted odds ratio [AOR]=0.23; 95% CI 0.06 - 0.82), but not Toronto (AOR=0.27; 95% CI 0.07 - 1.03), had lower odds of unsuppressed VL, compared to Montreal, as did older participants (AOR 0.93 per year; 95% CI 0.89 - 0.97), those at high-risk for hazardous drinking (AOR=0.19; 95% CI 0.05 - 0.70), those with a primary care provider (AOR=0.11; 95% CI 0.02 - 0.57), and those ever diagnosed with other STIs (AOR=0.12; 95% CI 0.04 - 0.32).

**Conclusion:** GBM living in Montreal, Toronto and Vancouver are highly engaged in HIV testing and treatment and all three cities have largely achieved the 90-90-90 targets for GBM. Nevertheless, we identified disparities which can be used to identify GBM who may require additional interventions to maximize HIV treatment benefits, in particular younger men and those who are without a regular primary care provider.

**Table:** Logistic regression analysis of factors associated with having a VL  $\geq 200$  copies/mL among 421 participants living with HIV in the Engage Study

|   |                            | Univariable |        | Multivariable |        |      |      |
|---|----------------------------|-------------|--------|---------------|--------|------|------|
|   |                            | Odds Ratio  | 95% CI | Adjusted OR   | 95% CI |      |      |
| Age                                     | Montreal                   | 0.94        | 0.91   | 0.97          | 0.93   | 0.89 | 0.97 |
|   | Toronto                    | Ref         |        |               | Ref    |      |      |
|   | Vancouver                  | 0.36        | 0.12   | 1.10          | 0.27   | 0.07 | 1.03 |
| Has a primary healthcare provider       |                            | 0.22        | 0.07   | 0.73          | 0.23   | 0.06 | 0.82 |
|   | Ever diagnosed with an STI | 0.08        | 0.02   | 0.25          | 0.11   | 0.02 | 0.57 |
| HADS score, Anxiety sub-scale           |                            | 0.16        | 0.07   | 0.35          | 0.12   | 0.04 | 0.32 |
| Used methamphetamine in past six months |                            | 1.11        | 1.03   | 1.19          |        |      |      |
| AUDIT C Scale Low Risk (score <4)       |                            | 1.04        | 0.41   | 2.64          |        |      |      |
| High Risk (score $\geq 4$ )             | Ref                        |             |        |               | Ref    |      |      |
|   |                            | 0.23        | 0.07   | 0.75          | 0.19   | 0.05 | 0.70 |

HADS = Hospital Anxiety and Depression Scale

**776 HIV CASCADE OF CARE AMONG MEN WHO HAVE SEX WITH MEN IN CANADA'S 3 LARGEST CITIES**

**David Moore**<sup>1</sup>, Zishan Cui<sup>1</sup>, Shayna Skakoon-Sparling<sup>2</sup>, Jordan Sang<sup>1</sup>, Justin Barath<sup>1</sup>, Lu Wang<sup>1</sup>, Nathan Lachowsky<sup>3</sup>, Joseph Cox<sup>4</sup>, Gilles Lambert<sup>5</sup>, Syed W. Noor<sup>2</sup>, Daniel Grace<sup>6</sup>, Jody Jollimore<sup>7</sup>, Alan Lal<sup>1</sup>, Trevor Hart<sup>2</sup>  
<sup>1</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada, <sup>2</sup>Ryerson University, Toronto, Canada, <sup>3</sup>University of Victoria, Victoria, Canada, <sup>4</sup>McGill University, Montreal, Canada, <sup>5</sup>McGill University Health Centre, Montreal, Canada, <sup>6</sup>University of Toronto, Toronto, Canada, <sup>7</sup>Community Based Research Centre, Vancouver, Canada

**Background:** Treatment as prevention strategies have been variously applied across provinces in Canada. We estimated HIV care cascade indicators and correlates of unsuppressed viral load (VL) among gay, bisexual and other men who have sex with men (GBM) recruited in Montreal, Toronto and Vancouver.

**Methods:** Sexually active GBM, aged  $\geq 16$  years, were recruited through respondent-driven sampling (RDS) from February 2017 to August 2019. Participants completed a Computer-Assisted Self-Interview and tests for HIV and other sexually transmitted infections (STIs). We conducted bivariate analyses comparing RDS-adjusted proportions across cities. The p values generated refer any significant difference across the three cities. We used multivariable logistic regression to examine factors associated with having a VL  $\geq 200$  copies/mL with data pooled from all three cities.

**777 REDUCTION IN INFECTIOUS SARS-CoV-2 IN TREATMENT STUDY OF COVID-19 WITH MOLNUPIRAVIR**



**Wendy P. Painter**<sup>1</sup>, Timothy Sheahan<sup>2</sup>, Ralph Baric<sup>2</sup>, Wayne Holman<sup>1</sup>, John Donovan<sup>3</sup>, Lei Fang<sup>3</sup>, Paul Alabanza<sup>2</sup>, Joseph J. Eron<sup>2</sup>, Erin Goecker<sup>4</sup>, Robert Coombs<sup>4</sup>, William Fischer<sup>2</sup>

<sup>1</sup>Ridgeback Biotherapeutics, LP, Miami, FL, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>Pharstat Inc, Raleigh, NC, <sup>4</sup>University of Washington, Seattle, WA, USA

**Background:** The emergence of SARS-CoV-2 viral variants threatens current anti-viral and preventative strategies, including monoclonal antibodies and vaccines. Critically, the limited supply of vaccines and the complex logistics surrounding the delivery of infusion-based therapies herald the need for an easily produced, distributed, and specific direct-acting antiviral for COVID-19 that limits progression of illness and ideally prevents transmission.

**Methods:** The efficacy of molnupiravir was evaluated in a double-blind, randomized, placebo-controlled, Phase 2 dose-range finding study using realtime polymerase chain reaction (RT-PCR) and virus isolation was conducted at 11 study sites in the U.S.

Participants were randomized if they had signs or symptoms of COVID-19 within 7 days, and a positive SARS-CoV-2 RT-PCR within 4 days of enrollment. Initially, participants were randomized in a 1:1 ratio to receive 200 mg molnupiravir or placebo twice daily for 5 days. Subsequently, in the dose-range finding portion of the study, participants were randomized in a 3:1 ratio to receive 200, 400, or 800 mg molnupiravir or placebo twice daily for 5 days. Nasopharyngeal swabs were analyzed from 175 subjects at enrollment, Day 3, and Day 5 for SARS-CoV-2 infectivity. Samples were stored at 4°C for up to 72 hours, shipped refrigerated, aliquoted, and stored at -80°C until testing. Vero E6 cell monolayers were infected with the sample for 1 hour. Culture medium was analyzed for viral load at 2 and 5 days post-infection by RT-PCR.

**Results:** Seventy-eight (45%) participants, median 4.62 days (min. 1.40, max. 7.54) from symptom onset, had a positive SARS-CoV-2 culture at enrollment (52 on active and 26 on placebo). The percentage of participants with a positive viral culture at enrollment who were positive on Day 3 was 20.4% on active and

28% on placebo ( $p = 0.56$ ). At day 5, 24% of placebo participants were culture-positive compared to none treated with molnupiravir ( $p = 0.001$ ). Between treatment, comparisons were performed using Fisher's exact test.

**Conclusion:** This is the first demonstration of reduced infectiousness by antiviral therapy in people with SARS-2 infection. This simple, short-course oral therapy may benefit individuals and public health and is unlikely to be impacted by spike-protein variants.

# DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH INELIGIBLE COMPANIES

Disclosure information is provided generally as submitted by the corresponding presenting abstract author, invited speaker, session moderator, or member of the CROI Program Committee. The below disclosures include financial relationships of any dollar amount with ineligible companies for themselves and their spouses or partners, as well as funding provided to their institutions. The Accreditation Council for Continuing Medical Education defines ineligible companies (formerly commercial interests) as “those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.”

## Acosta, Rima K.

**Self:** Employee of Gilead Sciences, Inc.; Stock/stock options from Gilead Sciences, Inc.

## Adimora, Adaora

**Self:** Consulting or advisor fees from Merck & Co., Inc., Gilead Sciences, Inc.; Research grant/grant pending from Gilead Sciences, Inc.; Speaker's bureau for Gilead Sciences, Inc.

## Alcaide, Maria L.

**Self:** Speaker's bureau for Merck & Co., Inc.

## Alter, Galit

**Self:** Employee of Seromyx Systems, Inc.; Research grant/grant pending from Gilead Sciences, Inc., Merck & Co., Inc., Sanofi, CureVac, Janssen Therapeutics, Novavax, Inc., Bristol Myers Squibb, GlaxoSmithKline, Pfizer Inc.

## Antinori, Andrea

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Merck & Co., Inc., ViiV Healthcare, Janssen Therapeutics, Roche, Theratechnologies Inc.; Research grant/grant pending from Gilead Sciences, Inc., ViiV Healthcare, Janssen-Cilag

## Arribas, Jose R.

**Self:** Consulting or advisor fees from ViiV Healthcare, Janssen Therapeutics, Gilead Sciences, Inc., Merck Sharp & Dohme, Teva, Alex, Serono; Research grant/grant pending from ViiV Healthcare, Gilead Sciences, Inc.

## Averitt, Dawn

**Self:** Consulting or advisor fees from Merck & Co., Inc., Gilead Sciences, Inc.

## Bekerman, Elena

**Self:** Stock/stock options from Gilead Sciences, Inc.

## Bekker, Linda-Gail

**Self:** Consulting or advisor fees from Johnson & Johnson, Merck Sharp & Dohme, Gilead Sciences, Inc.

## Benn, Paul

**Self:** Employee of ViiV Healthcare; Stock/stock options from GlaxoSmithKline

## Benson, Constance A.

**Self:** Consulting or advisor fees from GlaxoSmithKline, ViiV Healthcare, NDA Partners, LLC; Research grant/grant pending paid to institution from Gilead Sciences, Inc.  
**Spouse or Partner:** Stock/stock options from CytoDyn, Antiva Biosciences, Arcturus Therapeutics; Data monitoring board for VIR Biotechnology, Merck & Co., Inc.; Consultant for Sempra Energy, AbbVie Inc.

## Benson, Paul

**Self:** Speaker's bureau for ViiV Healthcare

## Berenguer, Juan

**Self:** Research grant/grant pending from Merck Sharp & Dohme, ViiV Healthcare; Consulting or advisor fees from Merck Sharp & Dohme, Janssen Therapeutics, ViiV Healthcare; Speaker's bureau for Merck Sharp & Dohme, Gilead Sciences, Inc., ViiV Healthcare

## Berko, Jeff

**Self:** Research grant/grant pending from ViiV Healthcare

## Bhagani, Sanjay

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Merck Sharp & Dohme, Roche, ViiV Healthcare; Speaker's bureau for Gilead Sciences, Inc., ViiV Healthcare; Research grant/grant pending paid to institution from Gilead Sciences, Inc., Merck Sharp & Dohme, Roche

## Blish, Catherine A.

**Self:** Board member for Catamaran Bio; Board member for DeepCell, Inc.

## Boesecke, Christoph

**Self:** Consulting or advisor fees from AbbVie Inc., Janssen Therapeutics, Gilead Sciences, Inc., Merck Sharp & Dohme, ViiV Healthcare

## Bourgi, Kassem

**Self:** Research grant/grant pending from Gilead Sciences, Inc.; Consulting or advisor fees from Gilead Sciences, Inc.

## Cai, Yanhui

**Self:** Employee of Gilead Sciences, Inc.; Shares from Gilead Sciences, Inc.

## Calcagno,rea

**Self:** Research grant/grant pending from ViiV Healthcare, Gilead Sciences, Inc.; Consulting or advisor fees from ViiV Healthcare, Gilead Sciences, Inc., Merck Sharp & Dohme, Janssen-Cilag

## Calmy, Alexandra L.

**Self:** Research grant/grant pending paid to institution from AbbVie Inc., Gilead Sciences, Inc., ViiV Healthcare, Merck Sharp & Dohme

## Carlander, Christina

**Self:** Consulting or advisor fees from Fees from Gilead Sciences, Inc., Merck Sharp & Dohme, Mediaset, GlaxoSmithKline/ViiV Healthcare; Research grant/grant pending from Gilead Sciences, Inc.

## Chadwick, Ellen Gould

**Spouse or Partner:** Stock/stock options from AbbVie Inc.

## Chaisson, Richard E.

**Self:** Consulting or advisor fees from Sanofi  
**Spouse or Partner:** Stock/stock options from Merck & Co., Inc.

## Chew, Kara W.

**Self:** Research grant/grant pending from Merck Sharp & Dohme

## Chomont, Nicolas

**Self:** Research grant/grant pending from EMD Serono Inc.

## Cihlar, Tomas

**Self:** Employee of Gilead Sciences, Inc.; Stock/stock options from Gilead Sciences, Inc.

## Clement, Meredith Edwards

**Self:** Consulting or advisor fees from FHI360; Research grant/grant pending from Gilead Sciences, Inc.; Royalties UpToDate

## Coffin, John M.

**Self:** Consulting or advisor fees from ROME Therapeutics

## Colby, Donn J.

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Inc.

## Cortes, Claudia P.

**Self:** Consulting or advisor fees from Merck, ViiV; Speaker's bureau for Merck & Co., Inc.

## Cox, Stephanie

**Self:** Employee of Gilead Sciences, Inc.

## Crauvels, Herta

**Self:** Employee of Janssen Therapeutics

## Currier, Judith S.

**Self:** Consulting or advisor fees from Merck & Co, Inc.

## D'Antoni, Michelle L.

**Self:** Employee of Gilead Sciences; Stock/stock options from Gilead Sciences, Inc.

## Del Amo, Julia

**Self:** Other fees from ViiV Healthcare, Gilead Sciences, Inc., Merck Sharp & Dohme

## Diamond, Tracy Lauren

**Self:** Employee of Merck & Co., Inc.

## Dougan, Michael

**Self:** Board member for Neoleukin Therapeutics; Consulting or advisor fees from ORIC Pharmaceuticals, Partner Therapeutics, Moderna; Research grant/grant pending from Novartis; Stock/stock options from Neoleukin Therapeutics

**Spouse/Partner:** Research grant/grant pending from Eli Lilly and Company, BMS, Novartis; Stock/stock options from Kojin Therapeutics

## Dumond, Julie B.

**Self:** Research grant/grant pending paid to institution from Merck & Co., Inc.

## Dybul, Mark

**Self:** Board member for Enochian Biosciences, GreenLight Biosciences

## El-Sadr, Wafaa M.

**Self:** Consulting or advisor fees from Merck & Co., Inc.

## Eron, Joseph J.

**Self:** Consulting or advisor fees from Merck & Co, Inc., ViiV Healthcare, Gilead Sciences, Inc., Janssen

## Evering, Teresa

**Self:** Consulting or advisor fees from Tonix Pharmaceuticals

## Fletcher, Courtney V.

**Self:** Research grant/grant pending paid to institution from ViiV Healthcare

## Flexner, Charles W.

**Self:** Consulting or advisor fees from Merck & Co., Inc., Mylan, ViiV Healthcare; Expert Testimony Gilead Sciences, Inc.; Board member for Navigen; Stock/stock options from Navigen

## Ford, Susan L.

**Self:** Employee of GlaxoSmithKline

## Gagliardini, Roberta

**Self:** Consulting or advisor fees from Janssen Therapeutics, Gilead Sciences, Inc., ViiV Healthcare, Merck Sharp & Dohme; Grants for advisory board in ViiV Healthcare, Gilead Sciences, Inc., Janssen Therapeutics

## Golden, Matthew R.

**Self:** Research grant/grant pending from Hologic, Inc.

## Grennan, Troy

**Self:** Research grant/grant pending paid to institution from Merck Canada, Inc., Gilead Sciences, Inc.

## Grinspoon, Steven

**Self:** Consulting or advisor fees from ViiV, Theratechnologies Inc.; Research grant/grant pending from ViiV Healthcare, Gilead Sciences, Inc., Kowa Pharmaceuticals, Theratechnologies Inc.; Patents from Theratechnologies Inc.; Royalties paid to the institution from Theratechnologies Inc.

## Gross, Jessica M.

**Self:** Stock/stock options from Abbott Laboratories; Research grant/grant pending from OraSure

## Gumrukcu, Serhat

**Self:** Consulting or advisor fees from Enochian Biosciences; Stock/stock options from Enochian Biosciences, Frida Therapeutics

**Havli, Diane V.**

**Self:** Provision of medicine or equipment Abbott Laboratories

**Herrera, Carolina**

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Inc.

**Hileman, Corri Lynn O.**

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Theratechnologies Inc.

**Hillier, Sharon L.**

**Self:** Consulting or advisor fees from Pfizer, Hologic, Curatek Pharmaceuticals, Dare Pharmaceuticals; Board member for Merck & Co., Inc.; Research grant/grant pending paid to institution from Curatek, Becton Dickinson, Merck & Co., Inc., Lupin, Gilead Sciences, Inc.

**Hsue, Priscilla**

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Merck & Co., Inc.

**Hung, Chien-Ching**

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Inc., Merck & Co., Inc., ViiV Healthcare; Speaker's bureau for Gilead Sciences, Inc., ViiV Healthcare; Consulting or advisor fees from Gilead Sciences, Inc., ViiV Healthcare

**Hunt, Peter W.**

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Inc.; Travel reimbursement from Gilead Sciences, Inc., Merck & Co., Inc.; Consulting or advisor fees from ViiV Healthcare, Biotron, Longeveron; Speaker fees from Gilead Sciences, Inc.

**Ingiliz, Patrick**

**Self:** Research grant/grant pending from Gilead Sciences, Inc.; Speaker's bureau for Gilead Sciences, Inc., AbbVie Inc., ViiV Healthcare

**Iwasaki, Akiko**

**Self:** Consulting or advisor fees from InProTher, 4BIO, Adaptive Biotechnologies, Spring Discovery, Vedanta, Boehringer Ingelheim

**Jeffrey, Jerry L.**

**Self:** Employee of ViiV Healthcare; Stock/stock options from GlaxoSmithKline

**Kallewaard, Nicole**

**Self:** Employee of Eli Lilly and Company; Former employee of AstraZeneca; Stock/stock options from Eli Lilly and Company, AstraZeneca

**Spouse or Partner:** Employee of Eli Lilly and Company, AstraZeneca; Spouse stock: Eli Lilly and Company, AstraZeneca

**Kambugu, rew D.**

**Self:** Consulting or advisor fees from AbbVie Inc., Merck Sharp & Dohme; Research grant/grant pending paid to institution from Pfizer Inc.

**Kandala, Bhargava**

**Self:** Employee of Merck & Co., Inc.; Stock/stock options from Merck & Co., Inc.

**Karn, Jonathan**

**Self:** Stock/stock options from AbbVie Inc., Bristol Myers Squibb, Editas Medicine, Fate Therapeutics, Gilead Sciences, Inc., Illumina, Inc., Medtronic, Moderna, Regeneron Pharmaceuticals, RSM, Vertex Pharmaceuticals

**Kashuba, Angela**

**Self:** Research grant/grant pending paid to institution from Merck & Co., Inc.

**Spouse or Partner:** Stock/stock options from Chimerix Inc.

**Klein, Marina B.**

**Self:** Consulting or advisor fees from ViiV Healthcare, Merck & Co., Inc., AbbVie Inc., Gilead Sciences, Inc.; Research grant/grant pending paid to institution from ViiV Healthcare, Merck & Co., Inc., Gilead Sciences, Inc.

**Koss, Catherine A.**

**Self:** Research grant/grant paid to institution from Gilead Sciences, Inc.

**Krystal, Mark**

**Self:** Employee of ViiV Healthcare; Stock/stock options from GlaxoSmithKline

**Kumar, Princy N.**

**Self:** Consulting or advisor fees from Ecargo, Amgen, GlaxoSmithKline, Gilead Sciences, Inc., Theratechnologies Inc.; Research grant/grant pending from Gilead Sciences, Inc.,

Theratechnologies Inc., Merck & Co., Inc., Amgen; Stock/stock options from Merck & Co., Inc., Gilead Sciences, Inc., Pfizer Inc., Johnson & Johnson

**Kuniholm, Mark H.**

**Self:** Consulting or advisor fees from Sanofi

**Lacombé, Karine**

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Merck Sharp & Dohme, Janssen Therapeutics, ViiV Healthcare, AbbVie Inc.

**Landovitz, Raphael J.**

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Merck & Co., Inc.; Speaker's bureau for Jansen Therapeutics, Roche

**Letendre, Scott**

**Self:** Research grant/grant pending from Merck & Co., Inc.

**Liu, Albert**

**Self:** Research grant/grant pending from Gilead Sciences, ViiV Healthcare; Other relationship(s) with Gilead Sciences, Inc.

**Libre, Josep Maria**

**Self:** Board member for ViiV Healthcare, Gilead Science, Inc., Janssen Therapeutics

**Lo, Janet**

**Self:** Consulting or advisor fees from ViiV Healthcare, Gilead Sciences, Inc.; Research grant/grant pending paid to institution from ViiV Healthcare

**Luetkemeyer, Annie**

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Inc., Merck & Co., Inc., Eli Lilly and Company

**Lurain, Kathryn**

**Self:** Research grant/grant pending paid to institution from Celgene-Bristol Myers Squibb, Merck & Co., Inc., EMD Serono Inc.

**Lutz, Justin**

**Self:** Employee of Gilead Sciences, Inc.; Stock/stock options from Gilead Sciences, Inc.

**Lyons, Michael S.**

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Inc.

**Macatangay, Bernard**

**Self:** Research grant/grant pending from Gilead Sciences, Inc.

**Magombedze, Gesham**

**Self:** Employee of Gilead Sciences; Stock/stock options from Gilead Sciences, Inc.

**Martin, Natasha**

**Self:** Research grant/grant pending from Merck & Co., Inc., Gilead Sciences, Inc.

**Martins, Mauricio A.**

**Self:** Board member for Emune, Inc.; Consulting or advisor fees from Emune, Inc.

**Martinson, Neil A.**

**Self:** Research grant/grant pending paid to institution from Pfizer Inc., Roche

**Matthews, Randolph P.**

**Self:** Employee of Employed by Merck & Co., Inc.

**Maury, Wendy**

**Self:** Research grant/grant pending from BerGenBio ASA, Stine Seed

**McCluskey, Suzanne**

**Self:** Research grant/grant pending from Gilead Sciences, Inc.

**McComsey, Grace A.**

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Merck & Co., Inc., ViiV Healthcare, Janssen Therapeutics; Research grant/grant pending paid to institution from Merck & Co., Inc., ViiV Healthcare, Gilead Sciences, Inc., Tetrphase, Roche, Astellas

**Melvin, Ann J.**

**Self:** Research grant/grant pending paid to institution from Merck & Co., Inc., Gilead Sciences, Inc.

**Millett, Greg A.**

**Self:** Speaker's bureau for Gilead Sciences, Inc.

**Miro, Jose M.**

**Self:** Research grant/grant pending paid to institution from ViiV Healthcare

**Mitchell, Kate M.**

**Self:** Speaker's bureau for Gilead Sciences, Inc.

**Moldt, Brian**

**Self:** Employee of Gilead Sciences, Inc.; Stock/stock options from Gilead Sciences, Inc.

**Molina, Jean-Michel**

**Self:** Research grant/grant pending from Gilead Sciences, Inc.; Board member for Gilead Sciences, Inc., Merck & Co., Inc., ViiV Healthcare, Aelix, Janssen Therapeutics, Sanofi

**Mothe, Beatriz**

**Self:** Consulting or advisor fees from Aelix Therapeutics SL

**Mounzer, Karam**

**Self:** Research grant/grant pending from Gilead Sciences, Inc., Merck & Co., Inc., Janssen Therapeutics, GlaxoSmithKline/ViiV Healthcare; Speaker's bureau for Gilead Sciences, Inc., Merck & Co., Inc., Janssen Therapeutics, GlaxoSmithKline/ViiV Healthcare; Board member for EpiVidian

**Mozaffari, Essy**

**Self:** Employee of Gilead Sciences

**Mulligan, Mark**

**Self:** Consulting or advisor fees from Meissa Vaccines, Inc.; Research grant/grant pending from Eli Lilly and Company, Pfizer Inc.

**Nakalema, Shadia**

**Self:** Research grant/grant pending from Janssen Pharmaceuticals

**Ndhlovu, Lishomwa**

**Self:** Consulting or advisor fees from AbbVie Inc., Cytodyn

**Neuzil, Kathleen**

**Self:** Research grant/grant pending paid to institution from Pfizer Inc.

**Nuermberger, Eric**

**Self:** Research grant/grant pending from Janssen

**O'Brien, Meagan P.**

**Self:** Employee of Regeneron Pharmaceuticals, Inc.

**Olender, Susan**

**Self:** Research grant/grant pending from Gilead Sciences, Inc. **Spouse or Partner:** Consulting or advisor fees from Tocagen, Synaptive Medical, Monteris, Robeate

**Orkin, Chloe**

**Self:** Research grant/grant pending from Gilead Sciences, Inc., Janssen Therapeutics, Merck Sharp & Dohme, ViiV Healthcare; Speaker's bureau for Gilead Sciences, Inc., Janssen Therapeutics, Merck Sharp & Dohme, ViiV Healthcare

**Painter, Wendy P.**

**Self:** Employee of Biotherapeutics LP

**Palella, Frank**

**Self:** Speaker's bureau for Gilead Sciences, Inc., Janssen Therapeutics, ViiV Healthcare, Merck & Co., Inc.

**Patel, Munjal**

**Self:** Employee of Merck & Co., Inc.; Stock/stock options from Merck & Co., Inc.

**Patel, Parul**

**Self:** Employee of ViiV Healthcare; Stock/stock options from GlaxoSmithKline

**Paton, Nicholas**

**Self:** Research grant/grant pending paid to institution from Janssen Therapeutics

**Perez-Valero, Ignacio**

**Self:** Consulting or advisor fees from ViiV Healthcare, Gilead Sciences, Inc., Merck Sharp & Dohme, Janssen Therapeutics; Research grant/grant pending from Janssen Therapeutics, ViiV Healthcare, Gilead Sciences, Inc.; Speaker's bureau for Gilead Sciences, Inc., Janssen Therapeutics, ViiV Healthcare, Merck Sharp & Dohme

**Phanuphak, Nittaya**

**Self:** Consulting or advisor fees from Merck Sharp & Dohme, ViiV Healthcare; Research grant/grant pending from Gilead Sciences, Inc.; Speaker's bureau for Gilead Sciences, Inc.

**Phillips, Tamsin Kate**

**Self:** Provision of medicine or equipment Abbott Laboratories

**Pickett, James**

**Self:** Program funding paid to organization from Gilead Sciences, Inc., Merck & Co., Inc.; Consulting or advisor fees from ViiV Healthcare

**Pinnetti, Carmela**

**Self:** Speaker's bureau for Gilead Sciences, Inc.; Speaker's bureau for Janssen-Cilag

**Podzamczak, Daniel**

**Self:** Research grant/grant pending from Gilead Sciences, Inc., Merck Sharp & Dohme; Consulting or advisor fees from Gilead Sciences, Inc., Merck Sharp & Dohme, ViiV Health Care, Janssen Therapeutics; Speaker's bureau for Gilead Sciences, Inc., Merck Sharp & Dohme, ViiV Healthcare, Janssen Therapeutics

**Post, Frank A.**

**Self:** Speaker's bureau for Gilead Sciences, Inc., ViiV Healthcare, Merck Sharp & Dohme, Janssen Therapeutics; Research grant/grant pending paid to institution from Gilead Sciences, Inc., ViiV Healthcare, Merck Sharp & Dohme, Janssen Therapeutics

**Poteat, Tonia**

**Self:** Research grant/grant pending from Gilead Sciences, Inc., ViiV Healthcare

**Protzer, Ulrike**

**Self:** Research grant/grant pending from AliOS, VIR Biotechnology, Roche; Consulting or advisor fees from Gilead Sciences, Inc., Leukocare AG, Merck Sharp & Dohme, GlaxoSmithKline, AbbVie Inc., Vaccitech, Dicerna

**Ramaswami, Ramya**

**Self:** Research grant/grant pending paid to institution from Celgene, Bristol Meyer Squibb; Research grant/grant pending paid to institution from Merck & Co., Inc.; Research grant/grant pending paid to institution from EMD Serano Inc.

**Reddy, Sai**

**Self:** Consulting or advisor fees from deepCDR Biologics AG

**Reiss, Peter**

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Inc., ViiV Healthcare, Merck & Co., Inc.; Board member for Gilead Sciences, Inc., ViiV Healthcare, Merck & Co., Inc.

**Richman, Douglas D.**

**Self:** Consulting or advisor fees from Antiva Biosciences, Gilead Science, Inc., Viriome, Inc.

**Rockstroh, Jürgen K.**

**Self:** Consulting or advisor fees from Abivax, Gilead Science, Inc., Merck & Co., Inc., and ViiV Healthcare; Speaker's bureau for Gilead Science, Inc., Merck & Co., Inc., and ViiV Healthcare

**Safrit, Jeffrey T.**

**Self:** Employee of NantKwest, Inc.

**Samanovic-Golden, Marie I.**

**Self:** Other laboratory and/or clinical trial contracts with Eli Lilly and Company, Pfizer Inc., Sanofi; Consulting or advisor fees from Meissa Vaccines, Inc., Pfizer Inc.

**Sanz, Ignacio**

**Self:** Consulting or advisor fees from GlaxoSmithKline, Janssen Therapeutics, Kyverna, Pfizer Inc., Visterra; Research grant/grant pending from GlaxoSmithKline

**Sax, Paul E.**

**Self:** Consulting or advisor fees from GlaxoSmithKline/ViiV Healthcare, Janssen Therapeutics, Merck & Co, Inc., Gilead Sciences, Inc.; Research grant/grant pending paid to institution

from Gilead Sciences, Inc., GlaxoSmithKline/ViiV

**Scarsi, Kimberly K.**

**Self:** Research grant/grant pending from Merck & Co, Inc.

**Scevola, Sofia**

**Self:** Research grant/grant pending from Merck Sharp & Dohme; Expert Testimony Merck Sharp & Dohme, ViiV Healthcare

**Schooley, Robert T.**

**Self:** Stock/stock options from CytoDyn, Antiva Biosciences, Arcturus Therapeutics; Consulting or advisor fees from VIR Biotechnology, Merck & Co, Inc., Semptra Energy, AbbVie Inc.

**Spouse or Partner:** Consulting or advisor fees from GlaxoSmithKline/ViiV Healthcare; Research grant paid to institution from Gilead Sciences, Inc.

**Serrano-Villar, Sergio**

**Self:** Research grant/grant pending paid to institution from Merck Sharp & Dohme, Gilead Sciences, Inc., ViiV Healthcare; Consulting or advisor fees from Gilead Sciences, Inc.; Speaker's bureau for Gilead Sciences, Inc., Merck Sharp & Dohme, Janssen Therapeutics

**Shafer, Robert W.**

**Self:** Research grant/grant pending from Unrestricted grant received from InSilixa, Inc

**Shapiro, Adrienne E.**

**Self:** Research grant/grant pending paid to institution from VIR Biotechnology

**Sharma, Amit**

**Self:** Patent # 63/106,689 USPTO

**Sherman, Kenneth E.**

**Self:** Research grant/grant pending from AbbVie Inc., Gilead Sciences, Inc., Intercept; Consulting or advisor fees from Theratechnologies Inc., Uniqure, Inovio, MedPace, Watermark; Royalties UpToDate

**Short, William R.**

**Self:** Research grant/grant pending from Viiv; Consulting or advisor fees from ViiV Healthcare, Janssen Therapeutics

**Silverberg, Michael J.**

**Self:** Research grant/grant pending from Gilead Sciences, Inc.

**Smith, Davey M.**

**Self:** Consulting or advisor fees from Arena Pharmaceuticals, Bayer Pharmaceuticals, Kiadis Pharmaceuticals; Stock/stock options from FluxErgy, Linear Therapies, Safe Aloha

**Sohn, Annette H.**

**Self:** Research grant/grant pending paid to institution from ViiV Healthcare

**Solomon, Sunil S.**

**Self:** Research grant/grant pending paid to institution from Gilead Sciences, Abbott Diagnostics; Speaker's bureau for Gilead Sciences, Inc.

**Spinner, Christoph**

**Self:** Consulting or advisor fees from AbbVie, Gilead, Molecular Partners, Formycon, Janssen, Merck Sharp & Dohme, ViiV Healthcare; Speaker's bureau for Gilead, Janssen, ViiV Healthcare; Research grant/grant pending from Gilead Sciences, Inc., Janssen Therapeutics, ViiV Healthcare

**Suzuki, Kazuo**

**Self:** Research grant/grant pending paid to institution from Denka Co. Ltd; Research grant/grant pending from Denka Co. Ltd, PlexBio Co Ltd; Research grant/grant pending from Denka Co. Ltd PlexBio Co Ltd

**Thomas, David L.**

**Self:** Consulting or advisor fees from Merck & Co., Inc., Excision Bio

**Tseng, Alice**

**Self:** Consulting or advisor fees from Gilead Sciences, Inc., Merck & Co., Inc., ViiV Healthcare; Research grant/grant pending paid to institution from Merck & Co., Inc., Gilead Sciences, Inc.

**Uldrick, Thomas S.**

**Self:** Consulting or advisor fees from AbbVie Inc., Seattle Genetics; Patents from Celgene/BMS; Research grant/grant pending from Roche, Merck & Co., Inc.

**Utay, Netanya Sandler**

**Self:** Relationship with EnteraHealth

**VanderVeen, Laurie**

**Self:** Employee of Gilead Sciences

**Vandyck, Koen**

**Self:** Employee of Aligos Belgium BV; Stock/stock options from Aligos Therapeutics, Inc.

**Venter, Francois**

**Self:** Speaker's bureau for Gilead Sciences, Inc., ViiV Healthcare, Mylan, Merck & Co., Inc., Adcock-Ingram, Aspen, Abbott Laboratories, Roche, Johnson & Johnson, Virology Education; Research grant/grant pending from ViiV Healthcare, Merck & Co., Inc.

**Vergori, Alessandra**

**Self:** Speaker's bureau for Janssen Therapeutics, Merck Sharp & Dohme; Research grant/grant pending from Gilead Sciences, Inc.

**Wedemeyer, Heiner**

**Self:** Consulting or advisor fees from Abbott Laboratories, AbbVie Inc., Altimune, Biotest, Bristol Myers Squibb, Dicerna Pharmaceuticals, Gilead Sciences, Inc., Janssen Therapeutics, MYR GmbH, Novartis, Roche, Siemens; Research grant/grant pending from Abbvie Inc., Biotest, Bristol Myers Squibb, Gilead Sciences, Inc., Merck Sharp & Dohme, Novartis, Transgene; Speaker's bureau for Abbvie Inc., Biotest, Janssen Therapeutics, Merck Sharp & Dohme; Clinical trials investigator Abbvie Inc., Altimune, Bristol Myers Squibb, Gilead Sciences, Inc., Janssen Therapeutics, Merck Sharp & Dohme, MYR GmbH, Novartis, Transgene

**Zhou, Xiao-Jian**

**Self:** Employee of and shareholder at Atea Pharmaceuticals

## THE FOLLOWING HAVE NO RELEVANT FINANCIAL RELATIONSHIPS TO DISCLOSE. ANY UPDATES WILL BE REFLECTED IN THE MOBILE APP.

Abraham, Natasha  
 Abrams, Elaine J.  
 Acharya, Arpan  
 Adeniji, Opeyemi Samson  
 Adhanom Ghebreyesus, Tedros  
 Allavena, Clotilde  
 Alrubayyi, Aljawharah Saleh Z.  
 Amara, Dominic  
 Amico, K. Rivet  
 Anderson, Albert M.  
 Anderson, Katherine M.  
 Anokhin, Boris  
 Antar, Annukka A.R.  
 Archary, Moherndran  
 Arora, Priyanka  
 Arts, Eric J.  
 Astorga Gamaza, Antonio  
 Athale, Janhavi  
 Attia, Engi F.  
 Ayala-Suarez, Ruben A.  
 Bailin, Samuel  
 Baker, Owen R.  
 Banga, Riddhima  
 Bansal-Matharu, Loveleen  
 Bar, Katharine J.  
 Barbera, Lauren K.  
 Barnabas, Ruanne  
 Barnes, Christopher O.  
 Bassett, Ingrid V.  
 Bassett, Mary T.  
 Bauermeister, José A.  
 Baxevanidi, Evangelia Eva  
 Bayer, Cara  
 Béguelin, Charles  
 Bekker, Adrie  
 Bender Ignacio, Rachel A.  
 Bengtson, Angela  
 Berendam, Stella J.  
 Bernard, Caitlin  
 Bester, Stephanie Marie  
 Bhatta, Manasa R.  
 Bien-Gund, Cedric  
 Birabahaman, Morgan  
 Biradar, Shivkumar  
 Bischoff, Jenny  
 Bjorkman, Pamela J.  
 Blanch-Lombarte, Oscar  
 Blanco, Jose L.  
 Blumenthal, Jill  
 Bogorodskaya, Milana  
 Bole, Medhavi  
 Booton, Ross D.  
 Borges, Monica  
 Borquez, Annick  
 Boswell, Kristin L.  
 Botha, Johannes C.  
 Brenner, Bluma G.  
 Bricker, Katherine M.  
 Brown, Jennifer A.  
 Buchbinder, Susan P.  
 Buggert, Marcus  
 Bunglawala, Fazila Sadik  
 Burgess, Jacqueline  
 Burgos-Cibrian, Joaquin  
 Busca Arenzana, Carmen  
 Bygrave, Helen  
 Calantone, Nina  
 Campbell, Edward  
 Capoferri, Adam A.  
 Capparelli, Edmund  
 Carmeliet, Peter  
 Carrasco, Itziar  
 Carrasco-Hernandez, Rocío  
 Carrico, Adam W.  
 Cartwright, Emily Jeanne  
 Casazza, Joseph P.  
 Caskey, Marina  
 Castillo-Mancilla, Jose R.  
 Castor, Delivette  
 Cavallari, Eugenio Nelson  
 Cerrillo, Ildefonso Sanchez  
 Chaila, Mwate Joseph  
 Chaisson, Lelia H.  
 Chan, Phillip  
 Chang, David  
 Chang, Joy C.  
 Chaudhary, Omkar  
 Chen, Athena  
 Chen, Benjamin K.  
 Chen, Guan-Jhou  
 Cheung, Peter K.  
 Chiao, Elizabeth  
 Chibesa, Linda Mwila  
 Chinula, Lameck  
 Chiu, Chris Y.H.  
 Chohan, Bhavna  
 Ciocca, Emily T.  
 Clipman, Steven J.  
 Coelho, Lara  
 Cohen, Myron S.  
 Coiras, Mayte  
 Collazo-Rodriguez, Bryan J.  
 Collins, Lauren F.  
 Collora, Jack A.  
 Conner, Madelyn  
 Connolly, Stephen P.  
 Cooley, Sarah  
 Corma-Gomez, Anaís  
 Corritori, Suzana  
 Cossarini, Francesca  
 Cottura, Nicolas  
 Cotugno, Nicola  
 Council, Olivia D.  
 Cressey, Tim R.  
 Cresswell, Fiona  
 Curran, Kathryn  
 Cysique, Lucette A.  
 Daama, Alex  
 Dabis, François  
 Dai, Weiwei  
 Daly, Michele B.  
 Daniels, Christine Nicole  
 Dapp, Michael  
 Davy-Mendez, Thibaut  
 De Nicolò, Amedeo  
 De Waard, Liesl  
 Dean, Lorraine T.  
 Dear, Nicole  
 del Rio, Carlos  
 Delaney, Kevin P.  
 Desai, Jui  
 Dhokotera, Tafadzwa G.  
 Di Mascio, Michele  
 Di Nunzio, Francesca  
 Diallo, Karidia  
 Dias, Joana  
 Diaz, Ricardo S.  
 Dillon, Stephanie  
 Dinh, Vinh B.  
 Dirajlal-Fargo, Sahera  
 Dodd, Lori  
 Domínguez-Rodríguez, Sara  
 Doores, Katie J.  
 Dorosh, Michael Jon  
 Dorvil, Nancy  
 Dorward, Jienchi  
 Doshi, Rupali K.  
 Dossani, Zain Y.  
 Dovel, Kathryn  
 Drain, Paul K.  
 Drammeh, Bakary  
 Du, Li  
 Einkauf, Kevin B.  
 El Kamari, Vanessa  
 Ellis, Ronald J.  
 El-Nahal, Walid  
 Ennis, Nicole  
 Enugu, Ajay K.R.  
 Esmaeilzadeh, Elmira  
 Esteban-Cantos, Andrés  
 Farhadian, Shelli F.  
 Farooqi, Sadaf  
 Fatti, Geoffrey  
 Fatti, Geoffrey  
 Fauci, Anthony S.  
 Fernandez, Danielle  
 Fernandez-Fuertes, Marta  
 Filippidis, Paraskevas  
 Finzi, Andrés  
 Fisher, Katie  
 Fitch, Kathleen  
 Fojo, Anthony Todd  
 Fowler, Mary G.  
 Francesco, Bonfante  
 Frasca, Federica  
 Fray, Emily J.  
 Freed, Eric O.  
 Freeman, Jincong  
 Fuente-Soro, Laura  
 Fulcher, Jennifer A.  
 Fullilove, Robert E.  
 Fursa, Olga  
 Gabriel, Curtis Lee  
 Galagan, Sean  
 Gallardo, Christian M.  
 Gálvez, Cristina  
 Gandhi, Monica  
 Ganser-Pornillos, Barbie  
 Gantner, Pierre  
 Garber, David A.  
 Garcia-Cremades, Maria  
 Garcia-Mesa, Yoelvis  
 Garrido, Carolina  
 Geldmacher, Christof  
 Gharbharan, Arvind  
 Gianella, Sara  
 Girdwood, Sarah Joy  
 Giron, Leila B.  
 Glögl, Matthias  
 Gomba, Yolanda  
 Gonsalves, Gregg S.  
 Gonzalez-Serna, Alejandro  
 Gordon, David E.  
 Goswami, Suranjana  
 Grañana-Castillo, Sandra  
 Grant-McAuley, Wendy  
 Grau-Expósito, Judith  
 Groebner, Jennifer L.  
 Gudipati, Smitha  
 Guha, Debjani  
 Gulick, Roy M.  
 Gupta, Amita  
 Gutiérrez Chamorro, Lucía  
 Hahn, Beatrice H.  
 Hammonds, Jason E.  
 Hanley, Timothy  
 Hanna, David B.  
 Harris, Tiffany G.  
 Hartana, Ciputra Adijaya  
 Hassan, Fatima  
 Henny, Kirk Doulgas  
 Hensley, Kathryn S.  
 Herrmann, Yannis  
 Hikichi, Yuta  
 Hildreth, James E.K.  
 Hindley, Laura  
 Hirsch, Vanessa M.  
 Hoang, Timothy  
 Hoffman, Risa M.  
 Hoffmann, Christopher  
 Hoffmann, Eveline  
 Hough, Julie  
 Hoover, Karen W.  
 Hosek, Sybil  
 Howell, Pauline J.B.  
 Hsieh, Emily  
 Huang, Ya-Lin A.  
 Hulgán, Todd  
 Humes, Elizabeth  
 Hung, Rachel K.Y.  
 Hyle, Emily P.  
 Iqbal, Kashif  
 Irrinki, Alivelu M.  
 Irungu, Elizabeth  
 Islam, Jessica Y.  
 Ivanova Reipold, Elena  
 Iyer, Shilpa S.  
 Jacobs, Jana L.  
 Jacobson, Evin  
 Jaeger, Hans  
 Janes, Holly  
 Jao, Jennifer  
 Jha, Divya  
 Jiang, Wei  
 Jiang, Wenwen  
 Jo, Youngji  
 Jogiraju, Vamshi  
 Johnston, Carrie  
 Johnson, Kelly Anne  
 Jones, R. Brad  
 Jordans, Carljin  
 Joseph Davey, Dvora L.  
 Joseph, Patrice  
 Joseph, Sarah B.  
 Juegl, Boris  
 Kahn, Jeffrey  
 Kamilya, Moses R.  
 Kapoor, Andrew  
 Karuna, Shelly  
 Kasaie, Parastu  
 Kashanchi, Fatah  
 Kassinjee, Reshma  
 Katbi, Moses  
 Ke, Ruian  
 Kelly, Christine  
 Kelly, Erin  
 Kenny, Grace  
 Khaitan, Alka  
 Kigozi, Darix Ssebaggala  
 Kilpeläinen, Athina  
 Kim, H. Nina  
 Kim, Hae-Young  
 Kim, Sangwon F.  
 Kimura, Izumi  
 Kinuthia, John  
 Kinvig, Hannah  
 Kirchoff, Frank  
 Klock, Ethan  
 Knudsen, Andreas Dehlbæk  
 Kolson, Dennis L.  
 Koofhethile, Catherine K.  
 Korber, Bette  
 Koup, Richard A.  
 Kräusslich, Hans-Georg  
 Krishnan, Sonya  
 Kumari, Namita

- LaCourse, Sylvia  
 Lahiri, Cecile D.  
 Lake, Jordan  
 Lam, Jennifer O.  
 Landman, Roland  
 Lanièce Delaunay, Charlotte  
 Lankowski, Alexander  
 Lawrence, David S.  
 Lawrence, Scott P.  
 Leбина, Limakatso  
 Lee, Guinevere Q.  
 Lee, Ming Jie  
 Li, Chenglei  
 Li, Jun  
 Li, Linying  
 Li, Yijia  
 Lian, Xiaodong  
 Lima, Viviane D.  
 Lin, Xionghao  
 Linley, Laurie  
 Liroff, Kaitlin  
 Liu, Qingbo  
 Liyanage, Namal  
 Lobo, Judith Diane  
 Lockman, Shahin  
 Logan, Joseph E.  
 Luban, Jeremy  
 Lockett, Patrick H.  
 Lurie, Nicole  
 Lusi, Osborn  
 Luz, Paula M.  
 Lyall, Hermione  
 Ma, Jimmy  
 Mahajan, Supriya Dinkar  
 Mahwire, Tamirirashie Christopher  
 Makarova, Natalia  
 Malaba, Thokozile R.  
 Maldarelli, Frank  
 Malmström, Stina  
 Malone, Shawn T.  
 Mandelbrot, Laurent  
 Manmathan, Gavin  
 Manuzak, Jennifer A.  
 Maphosa, Thulani  
 Marin, Miguel  
 Martin, Charlene  
 Masip, Jenifer  
 Maskew, Mhairi  
 Massaccesi, Guido  
 Massana, Nuria  
 Massud, Ivana  
 Masters, Mary Clare C.  
 Mathad, Jyoti S.  
 Matthews, Gail  
 Matus Nicodemus, Rodrigo  
 Mazrouee, Sepideh  
 Mburu, Margaret  
 McCormack, Sheena  
 McCrary, Andrew  
 McFall, Allison M.  
 McGettrick, Padraig  
 McGinnis, Kathleen A.  
 McGinty, Tara  
 McIntyre, James  
 McMahan, Cynthia  
 Mellins, Claude A.  
 Menza, Timothy William  
 Mermin, Jonathan  
 Meyer, Megan F.  
 Mhlanga, Laurette  
 Michael, Benedict D.  
 Michel, Katherine G.  
 Minchella, Peter  
 Mitchell, Brooks  
 Mitchell, Julie  
 Mitsuyasu, Ronald T.  
 Moeng, Letumile R.  
 Molsberry, Samantha A.  
 Montanha, Maiara Camotti  
 Montes, Maria Luisa  
 Montoya, Vanessa R.  
 Moore, David  
 Moore, David J.  
 Moore, Penny  
 Morales, Ayana  
 Moran, Caitlin A.  
 Moysi, Eirini  
 Mugo, Nelly Rwamba  
 Müller, Barbara  
 Müller, Janis  
 Munoz, Flor  
 Mutambanengwe-Jacob, Mercy Tapiwa  
 Mutetwa, Tinaye  
 Myer, Landon  
 Nabukalu, Dorean  
 Naidoo, Dhirisha  
 Nandakumar, Bharat  
 Nansereko, Brendah  
 Nash, Denis  
 Nasuuna, Esther M.  
 Neary, Megan  
 Neesgaard, Bastian  
 Neilan, Anne M.  
 Nekhai, Sergei  
 Nematadzira, Teacler Gamuchirai  
 Nicolau, Ioana  
 Niu, Xin  
 Nouhin, Janin  
 Nyakato, Patience  
 Obregon-Perko, Veronica  
 Odayar, Jasantha  
 Ogbuagu, Onyema  
 O'Halloran, Jane  
 Okere, Nwanneka  
 Okhai, Hajra  
 Okoye, Afam  
 Omer, Saad  
 Omondi, Fredrick Harrison  
 Onyango, Dickens Otieno  
 Ortiz, Alexandra  
 Overbaugh, Julie  
 Pacheco Garcia, Vinicius  
 Pacheco-López, Yolanda María  
 Padmanabhan Chandrasekar, Aswath  
 Palanee-Phillips, Thesla  
 Pampena, M. Betina  
 Parisi, Saverio Giuseppe  
 Park, Lesley S.  
 Pascom, Ana Roberta Pati  
 Patel, Eshan U.  
 Pathak, Vinay K.  
 Pathela, Preeti  
 Paul, Robert  
 Pearson, Catherine  
 Pei, Luxin  
 Pena Dias, Jenny  
 Pereira Ribeiro, Susan  
 Pérez Yanes, Silvia  
 Pérez, Liliana  
 Person, Anna  
 Peruski, Anne H.  
 Peters, Brandilyn A.  
 Peters, Helen  
 Petersen, Kalen  
 Petrara, Maria Raffaella  
 Pettit, April  
 Philip, Neena M.  
 Phongsamart, Wanatpreeya  
 Pickering, R. Taylor  
 Piermatteo, Lorenzo  
 Pillay, Yogan  
 Pines, Heather A.  
 Pintye, Jillian  
 Piscitelli, Joseph  
 Plaza-Jennings, Amara  
 Pourcher, Valérie  
 Poveda, Eva  
 Pradenas, Edwards  
 Prata Menezes, Neia  
 Prelli Bozzo, Caterina  
 Premeaux, Thomas Alan  
 Price, Joan T.  
 Puntmann, Valentina O.  
 Puray-Chavez, Maritza N.  
 Rahman, Sheikh Abdul  
 Rana, Aadia  
 Rao, Shubha  
 Rasmussen, Thomas A.  
 Rawlings, Stephen A.  
 Rawson, Jonathan  
 Rhee, Soo-Yon  
 Rinaldi, Stefano  
 Riou, Julien  
 Robbins, Reuben N.  
 Roberts, Allen  
 Rodriguez-Centeno, Javier  
 Rodriguez-Hart, Cristina  
 Rolland, Morgane  
 Romo, Matthew L.  
 Ronen, Keshet  
 Rosa, Annachiara  
 Rosen, Elias  
 Rousseau, Elzette  
 Rousseau, Kimberly E.  
 Roxby, Alison C.  
 Ruffieux, Yann  
 Ruggiero, Alessandra  
 Ruiz-Mateos, Ezequiel  
 Sachathep, Karam  
 Safo, Sandra E.  
 SahBandar, Ivo  
 Sailasuta, Napapon  
 Salahuddin, Syim  
 Salazar-Austin, Nicole  
 Salters, Kate  
 Sánchez-Gaona, Nerea  
 Sannier, Gérémy  
 Santinelli, Letizia  
 Santoro, Maria Mercedes  
 Schmeisser, Hana  
 Schmidt, Haley  
 Schnittman, Samuel R.  
 Schnure, Melissa  
 Scholtes, Gael  
 Scholz, Erin M.B.  
 Scott, Hyman  
 Scully, Eileen P.  
 Seder, Robert  
 Segal-Maurer, Sorana  
 Sekaggya-Wiltshire, Christine  
 Sembajwe, Sophie  
 Sendagala, Samuel  
 Sereti, Irimi  
 Sessa, Libera  
 Sevenler, Derin  
 Shaw, Pamela A.  
 Sherman, Jessica P.  
 Shiau, Stephanie  
 Shikuma, Cecilia M.  
 Shoucri, Sherif  
 Shytaj, Iart Luca  
 Sibinga, Erica  
 Sibude, Jeanne  
 Siedner, Mark  
 Siegler, Aaron J.  
 Sigal, Alex  
 Sigel, Keith  
 Silhol, Romain  
 Silvestri, Guido  
 Simpson, Jennifer  
 Singh, Sonia  
 Singh, Vidisha  
 Sirajee, Reshma  
 Sirois, Patricia A.  
 Sjöland, Carl Fredrik  
 Sleeman, Katrina  
 Smith, Lauren  
 Solanky, Dipesh  
 Sparrer, Konstantin  
 Spearman, Paul  
 Spinelli, Matthew  
 Spudich, Serena S.  
 Srinivasula, Sharat  
 Sriudomporn, Salin  
 Stalter, Randy  
 Stephens, Jessica  
 Stockelman, Kelly Anne  
 Stoddard, Caitlin  
 Stumpp, Michael Tobias  
 Sullivan, Patrick S.  
 Sun, Hsin-Yun  
 Sun, Jing  
 Sun, Weiwei  
 Sundararajan, Radhika  
 Sundquist, Wesley I.  
 Surial, Bernard  
 Swaminathan, Souyma  
 Tagarro, Alfredo  
 Takuva, Simbarashe  
 Tanaka, Shiho  
 Tang, Michael E.  
 Tarancon-Diez, Laura  
 Tassi, Marc-Florent  
 Tedaldi, Ellen M.  
 Telwatte, Sushama  
 tenOver, Benjamin  
 Thiel, Volker  
 Thomas, Allison S.  
 Thudium, Rebekka Faber  
 Tinago, Willard  
 Tiraboschi, Juan M.  
 Titanji, Boghuma K.  
 Tokuyama, Minami  
 Tordoff, Diana M.  
 Toska, Elona  
 Townes, Ashley R.  
 Trautmann, Lydie  
 Trombetta, Amelia Chiara  
 Turkova, Anna  
 Udeagu, Chi-Chi N.  
 Udwardia, Zarir F.  
 Ueaphongsukkit, Thorntun  
 Upadhyay, Chitra  
 Vaccari, Linda Cheyenne  
 Van Lettow, Monique  
 Varshney, Karan  
 Veenhuis, Rebecca  
 Velu, Vijayakumar  
 Vidarsson, Gestur  
 Villanueva, Merceditas  
 Virga, James Q.  
 Volpe, Karen E.  
 Wagner, Gabriel  
 Wallner, Jackson J.  
 Wang, Melody  
 Watson, Dovie L.  
 WEISKOPF, DANIELA  
 Weiss, Kevin  
 Weissmann, Simon  
 White, Jennifer A.  
 Whittaker, Elizabeth A.  
 Wiche Salinas, Tomas Raul  
 Williams, Michelle  
 Wilson, David R.  
 Woldemeskel, Bezawit Abi  
 Woldesenbet, Selamawit A.  
 Wong, Emily B.  
 Wong, Michelle E.  
 Workowski, Kimberly  
 Wu, Yingfeng  
 Yacoub, Anne D.  
 Yager, Jenna Lynn  
 Yang, Jincheng  
 Yendewa, George A.  
 Yola, Ntando  
 Yu, Xu  
 Yuen, Kwok-Yung  
 Zacharopoulou, Penny  
 Zangeneh, Sahar Z.  
 Zanni, Markella V.  
 Zash, Rebecca  
 Zeuli, John D.  
 Zhang, Peng  
 Zhou, Shuntai  
 Zuck, Paul

# AUTHOR INDEX

- A–  
 Aarnoutse, Rob 90, 131  
 Abadir, Peter 536  
 Abbassi, Maggie 444  
 Abdel-Mohsen, Mohamed 114, 156, 282, 458  
 Abdelnabi, Rana 387  
 Abdi, Zakee 550  
 Abdo, Mona H 546  
 Abdool Karim, Quarraisha 649  
 Aber, Florence 90  
 Aberg, Judith A 219, 395, 494, 496, 498, 506  
 Aboud, Michael 417  
 Abraham, Alison G 626  
 Abraham, Natasha 610  
 Abramovitz, Daniela 652  
 Abrams, Elaine J 568, 590, 761  
 Abrams, Samuel David 234  
 Abreu, Celina 322  
 Abubakar, Abdulmalik 736, 774  
 Abulizi, Xian 537  
 Abuna, Felix 707, 710  
 Abuya, Dorcus 427  
 Acharya, Arpan 382  
 Achim, Cristian I 327  
 Ackerman, Peter 422  
 Acosta, Edward 607  
 Acosta, Rima K 415, 430, 438  
 Adalbert, Jenna 631  
 Adams, Andrew C 121, 122, 426  
 Adams, Dee 657  
 Adams, Lindsey 255  
 Adams, Scott V 474  
 Adan, Matthew Anthony 554  
 Adeagbo, Oluwafemi 753  
 Adedoyin, Adefisayo 736, 774  
 Adegboye, Adeoye 736, 774  
 Adelekan, Adeboye 675  
 Adeniji, Opeyemi Samsom 282  
 Adeyeye, Adeola 153  
 Adih, William 760  
 Adimora, Adaora 247, 526, 538, 539  
 Adisetiyo, Helty 272  
 Adler, Michelle 659, 720, 725, 763  
 Adu-Ampratwum, Daniel 420  
 Afzal, Shoaib 499  
 Aga, Evgenia 311, 555  
 Agajanian, Megan J 188  
 Agan, Brian 483  
 Agarwal, Smisha 694  
 Agarwal, Yash 200  
 Agil, Deana 626  
 Agnew Brune, Christine 677  
 Agolory, Simon 759  
 Agosto, Moises 418  
 Agrati, Chiara 242, 336  
 Aguilera-Alonso, David 581  
 Agyei, Yaw 678  
 Ahluwalia, Surbahi 580  
 Ahmad, Asrar 230  
 Ahmed, Amina 617  
 Ahmed, Mohamed I M 557  
 Ahmed, Rafi 157  
 Ahmed, Sarah 471  
 Ahn, Haelee 98, 254  
 Aholou, Tiffany 143  
 Ait-Khaled, Mounir 417  
 Aizire, Jim 567  
 Ajibola, Gbolahan 609  
 Akapirat, Siriwat 179  
 Akbarian, Schahram 342  
 Ake, Julie 519, 557, 732  
 Akinyi, Grace 435  
 Akpan, Asangaedem 365  
 Akullian, Adam 648  
 Alabanza, Paul 777  
 Alam, Munir S 268  
 Alarcón-Soto, Yovaninna 161  
 Alba, Verónica 194  
 Albano, Jessica D 584  
 Alber, Dagmar 491  
 Alcaide, Maria L 260  
 Alcamí, José 159, 228, 386  
 Aldrovandi, Grace M 221  
 Alejos, Belen 535  
 Alessandri-Gradt, Elodie 404  
 Alex, Muganzi 729  
 Alexander, Heather 435, 689  
 Alexeeff, Stacey E 97  
 Alfaro, Ricardo 252, 287  
 Alfranca, Arantzazu 216  
 Ali, Hammad 738  
 Alkhatib, Mohammad 137  
 Allavena, Clotilde 419, 537  
 Allen, Joseph M 119  
 Allen-Davidian, Yasmin 552  
 Allerton, Joanna 93  
 Allette, Kimaada 302  
 Al-Nahari, Mogebe 444  
 Alonso, Jose Antonio 620  
 Alrubayyi, Aljawharah Saleh Z 262  
 Alter, Galit 275  
 Althaus, Christian 139  
 Althoff, Keri N 102, 104, 456, 468, 503, 510, 626, 654, 670, 671  
 Altice, Frederick 740  
 Alto, Alecia 295  
 Alvarez, Beatriz 339  
 Álvarez, Hortensia 227  
 Alvarez, Jaylene 350  
 Alvarez, Jean-Claude 419  
 Alvarez, Jessica A 512  
 Alvarez, Julio 169  
 Alvarez-Barco, Elena 96  
 Alvarez-Hernández, Xavier 347  
 Amara, Dominic 467  
 Amara, Rama R 83, 157, 296, 583  
 Amat, Karine 419  
 Amberbir, Alemayehu 181  
 Ambrosioni, Juan 159  
 Ambrozak, David R 82, 192, 193  
 Amele, Sarah 443  
 Amendola, Alessandra 336  
 Amico, K Rivet 567, 603, 711, 713  
 Ammosova, Tatiana 198  
 Amodio, Donato 622  
 Amrine-Madsen, Heather 233  
 Amstutz, Alain 400, 431  
 Amstutz, Patrick 385  
 Ananthula, Hari Krishna 376  
 Ananworanich, Jintanat 154, 163, 179, 311, 323, 340, 359, 408, 595, 672  
 Anas, Adam A 392  
 Anastos, Kathryn 322, 526, 765  
 Ances, Beau M 164, 317, 319  
 Ancochea, Julio 216  
 Ancuta, Petronela 233  
 Anderegg, Nanina 615  
 Anderson, Albert M 324  
 Anderson, Alexandra 97  
 Anderson, Christy 248, 288  
 Anderson, Elizabeth 255  
 Anderson, Evan 621  
 Anderson, Katherine M 711  
 Anderson, Maija 718  
 Anderson, Megan 243  
 Anderson, Peter 92, 153, 354, 355, 366, 367, 398, 713  
 Andrade, Bruno B 559  
 Andrade-Villanueva, Jaime Federico 401  
 Andreatta, Kristen 438  
 Andreoni, Massimo 137  
 Andrews, Laurie 244  
 Andriesen, Jessica 257  
 Angeli, Leila 242  
 Ankrom, Wendy 376  
 Anokhin, Boris 80, 196  
 Anokye-Danso, Fredrick 515  
 Anson, Ryan 542  
 Antar, Annukka AR 209, 315  
 Anthony, Donald 135  
 Antinori, Andrea 242, 334, 336, 429, 545, 748  
 Antoli, Arnau 256  
 Antonelli, Guido 208  
 Antoniou, Tony 484  
 Anugulruengkitt, Supaporn 601  
 Aouizerat, Bradley 539  
 Apilanez, Miren Apilanez 597  
 Apollon, Alexandra 184  
 Apolot, Madina 173  
 Apostolou, Andria 108, 655  
 Apostolova, Nadezda 453  
 Appleton, Allison 538  
 Appolonia, Aoko 635  
 Aquino, Jhoanna Z 625  
 Aquino, Luis Martins 741  
 Ard, Kevin L 95  
 Ardeshir, Amir 270  
 Arenas-Pinto, Alejandro 492  
 Areson, Christine 728  
 Arif, Muhammad S 313  
 Armas, Laura 744  
 Armas, Lesley De 245, 246, 286  
 Armenia, Daniele 429  
 Armon, Carl 752  
 Armstrong, Wendy S 547  
 Arora, Priyanka 369  
 Arpadi, Stephen M 332  
 Arregui, Laura 256  
 Arribas, Jose R 453, 460, 534, 535, 544, 549  
 Arthur, Taryn 749  
 Arts, Eric J 267  
 Asante-Appiah, Ernest 129, 376  
 Asens, Victor 527  
 Asif, Sumbul 572  
 Asokan, Mangaiarkarasi 82  
 Assal, Frederic 343  
 Assoumou, Lambert 148, 419, 511  
 Astemborski, Jacquie 536  
 Astorga Gamaza, Antonio 207, 306  
 Asundj, Archana 514  
 Atkinson, Andrew 452  
 Atluri, Vidya 553  
 Atmar, Robert L 464  
 Attia, Engi F 611  
 Atukunda, Mucunguzi 151  
 Atzori, Cristiana 335  
 Augenbraun, Michael 247  
 Augusto, Orvalho 660  
 Auld, Andrew F 634, 746  
 Aurlpibul, Linda 604, 658  
 Avery, Ann K 501  
 Avettand-Fenoël, Véronique 570  
 Avihingsanon, Anchalee 135, 178, 370  
 Ávila-Nieto, Carlos 259  
 Ávila-Ríos, Santiago 251  
 Aweeka, Fran 98, 254  
 Awuonda, Benard 635  
 Ayala-Suarez, Ruben A 228  
 Ayalew, Kassahun 675  
 Aydemir, Serkan 231  
 Aydillo, Teresa 211  
 Aye, Pyone 84, 199  
 Ayieko, James 151  
 Ayles, Helen 678, 680, 682  
 Aylott, Alicia 489  
 Ayoub, Ahmed Taha 394  
 Azamfirei, Razvan 209  
 Azzad, Masoud 122  
 Azzizi, Hiva 267  
 Azman, Andrew S 746  
 Aabaasa, Andrew M. 1088  
 Abbink, Peter 145  
 Abdel-Mohsen, Mohamed 124, 304, 332, 385, 386  
 Abdelsamed, Hossam 313  
 Abdool Karim, Salim S. 53, 375  
 Abdul-Quader, Abu 845  
 Abduljawad, Sultan 29  
 Abdullah, Wailagala 748  
 Abdullahi, Adam 1061  
 Abebe, Kaleab 207  
 Aberg, Judith 213, 497, 899  
 Abernethy, Neil 1090, 1092  
 Abimiku, Alash'le 725  
 Ablanedo Terrazas, Yuria 266  
 Abou-Samra, Abdul-Badi 88  
 Aboud, Michael 144, 490, 679  
 Aboud, Said 555  
 Abraham, Alison 239, 240, 520  
 Abraham, Bisrat 1049  
 Abrahams, Melissa-Rose 375  
 Abram, Michael E. 370  
 Abrams, Elaine J. 462, 750, 751, 763, 764, 767, 785, 815, 819, 1008  
 Abrams, William 1051  
 Abu-Ali, Galeb 787  
 Abulizi, Xian 509  
 Abuna, Felix 778, 926, 961, 980, 993, 1082  
 Abuogi, Lisa L. 753  
 Abutu, Andrew 1009  
 Achalapong, Jullapong 629  
 Achenbach, Chad J. 258, 285  
 Achia, Thomas 94, 146, 1063  
 Achwoka, Dunstan 1063  
 Ackerman, Margaret 357  
 Ackerman, Peter 483  
 Acosta, Edward P. 26, 829  
 Acosta, Rima K. 551  
 Adachi, Eisuke 619  
 Adams, Debra R. 100, 970  
 Adams, Dee 981  
 Adams, Monica 844  
 Adams, Robert J. 212  
 Adams, Rodney S. 699  
 Adams, Scott V. 27  
 Adams, Stuart 809  
 Adams, Tiffany 903  
 Adams-Huet, Beverley 675  
 Adamson, Blythe J. 1075  
 Adamson, Lourdes 475  
 Adamu, Yakubu 517, 904  
 Addepalli, Balasubrahmanyam 378  
 Adelsberger, Joseph 727  
 Adeyeye, Adeola 34, 473, 912, 965, 995  
 Adimora, Adaora 15, 283, 672, 1068  
 Adje-Toure, Christiane 1033  
 Aerts, Joeri 389  
 Affolabi, Dissou 99  
 Affram, Yvonne 177  
 Afzal, Shoaib 638, 676  
 Aga, Evgenia 26  
 Agaba, Collins 934  
 Agaba, Patricia A. 606  
 Agan, Brian K. 316, 414  
 Agbaji, Oche 606  
 Agee, Tracy 587  
 Aglitti, Andrea 560  
 Agnew-Brune, Christine 920, 1078  
 Agopian, Anya 967  
 Agot, Kawango 1074  
 Agrahari, Vivek 101  
 Aguirrebengoa, Koldo 609  
 Agulló, Vanesa 524

- Aguwa, Merilyne 581  
 Agyei, Yaw 995  
 Agyemang, Elfriede 831  
 Ahlschlager, Lauren 955  
 Ahmadyar, Shekeba 480  
 Aho, Inka 565  
 Ahrens, Kym R. 1057  
 Ahumada, Adriana 562  
 Ait Si Selmi, Lamyia 744  
 Ajana, Faiza 985  
 Ajibola, Gbolahan 43, 781, 786, 797, 826  
 Ajose, Taiwo A. 572, 573  
 Ajulong, Caroline 959  
 Akapirat, Siriwat 293, 402  
 Akay-Espinoza, Cagla 435  
 Ake, Julie 517, 904, 977  
 Akelo, Victor 146  
 Akkina, Ramesh K. 475  
 Akpa, Samuel 606  
 Akpomiemie, Godspower 749  
 Akselrod, Hana 849  
 Akullian, Adam N. 1087  
 Al-Khouja, Amer 488  
 Al-Kindi, Sadeer 658  
 Alagaratnam, Jasmini 122  
 Alamo, Stella 959  
 Alary, Michel 99  
 Alba, Verónica 261, 267  
 Alba Alejandre, Irene 758  
 Albanesi, Edoardo 549  
 Albano, Jessica D. 747  
 Alber, Dagmar 646  
 Albillas, Agustín 562  
 Albrecht, Stefan 957, 990  
 Alcaide, Maria L. 1068  
 Alcamí Pertejo, José 363, 614  
 Aldámiz-Echevarría, Teresa 562  
 Aldrovandi, Grace M. 166, 229, 230  
 Alenyar, Yoko 201  
 Alexander, Heather 1033  
 Alexeeff, Stacey 105, 1044  
 Alfaro, Ricardo 521  
 Alger, Jeffrey 456  
 Alghamdi, Wael A. 825  
 Alinde, Berenice 322  
 Alizon, Samuel 594  
 Alkhasim, Chariff 318  
 Allard, Sabine 389  
 Allavena, Clotilde 275, 289, 493, 523, 984  
 Allen, Susan 1035  
 Alice, Tiziano 476  
 Almasri, Cassandra 28, 351  
 Alonso, Maria J. 294  
 Alsop, James 1026  
 Alston-Smith, Beverly 89  
 Alter, Galit 320  
 Altfeld, Marcus 374  
 Althoff, Keri N. 97, 671, 882, 893, 1023, 1089  
 Altice, Frederick 882, 1028, 1031  
 Alvarado, Gadiel 655  
 Alvarado, John 195  
 Alvarez, Alberto 458  
 Álvarez, Beatriz 571  
 Álvarez, Hortensia 218  
 Alvarez, Maria 582, 603, 604  
 Alvarez-Barco, Elena 689  
 Alvero, Carmelita 829  
 Alves, Deolinda 466  
 Alves Saldanha, Susana 466  
 Alwano, Mary Grace 1051  
 Amama, Sharon 775  
 Amara, Aliou 757  
 Amasio, Maria Enrica 476  
 Ambrose, Zandrea 71  
 Ambrozak, David R. 183, 351  
 Amgalan, Ariunzaya 586  
 Amico, K. Rivet 979, 1050  
 Amiel, Corinne 273, 867  
 Amone, Alexander 775  
 Amoruso, Daniela Caterina 566  
 Amstutz, Alain 1025  
 Amuge, Pauline 830  
 An, Ly Thanh. 845  
 An, Minghui 879  
 An, Tran Khanh 845  
 Anaedozie, Onyeka 587  
 Anand, Santhanam 1038  
 Ananthswamy, Neeti 364  
 Ananworanich, Jintanant 44, 298, 300, 350, 402, 404, 409, 416, 440, 444, 450, 457, 522, 801, 803, 820  
 Anastos, Kathryn 408, 663, 1001, 1023  
 Anato, Simplicio 910  
 Ances, Beau 123, 442, 453, 460  
 Ancuta, Petronela 245, 262, 301, 632  
 Anderegg, Nanina 1016  
 Anderson, Bridget J. 528  
 Anderson, Ellen 682  
 Anderson, Emeli Jane. 843, 971  
 Anderson, Jane 662, 698  
 Anderson, Jodi 103  
 Anderson, Megan 448  
 Anderson, Peter L. 463, 469, 477, 626, 657, 946, 987, 992, 995  
 Andersson, Sören 555  
 Ando, Dale 25  
 Andrade, Adriana 35, 129, 703  
 Andrade, Bruno 216  
 Andrade Villanueva, Jaime 492  
 Andrade-Villanueva, Jaime-Federico 139  
 Andreatta, Kristen 551, 552  
 Andreoni, Massimo 535, 607  
 Andrew, Philip 792  
 Andrews, Sarah F. 308  
 Angel, Jonathan 301, 393  
 Angert, Christine Doyle. 672  
 Angira, Francis 78  
 Annet, Onzia 748  
 Anok, Aggrey 425  
 Ansari, Aftab A. 970  
 Ansel, Jessica 145  
 Anteneh, Aderaw 1041  
 Anthony, Colin 375  
 Anthony, Donald D. 89  
 Anthony, Mark 837  
 Anthony-Gonda, Kim 359  
 Antinori, Andrea 502, 511, 535, 693, 911  
 Antonelli, Guido 174  
 Antoni, Guillemette 846, 960  
 Antonio, Marilia B. 1012  
 Antwi, Sampson 825  
 Anzures, Alitzel 124  
 Ao, Trong Tony. 951  
 Apornpong, Tanakorn 599, 808, 820  
 Appel, Scott 136  
 Appelmans, Eline 445  
 Appendino, Alice 549  
 Applegate, Tanya 577  
 Arabella, Bestetti 423  
 Arakelyan, Anush 326  
 Araripe Sucupira, Maria Cecilia 399  
 Arastéh, Keikawus 140  
 Arayasirikul, Sean 973  
 Arca-Lafuente, Sonia 600  
 Archange, Danie 720  
 Archibald, Chris 888  
 Archin, Nancie 375  
 Arduino, Roberto 145  
 Arenas-Pinto, Alejandro 651, 821  
 Arezes, Elisa 744  
 Argawal, Divyansh 134  
 Arif, Muhammad S. 399  
 Arimide, Dawit A. 536  
 Armenia, Daniele 535  
 Armon, Carl 30, 853  
 Armstrong, Hilary 583  
 Armstrong, Wendy S. 889  
 Arnold, Arinaitwe S. 748  
 Arpadi, Stephen M. 815, 816  
 Arribas, Jose Ramon. 492, 502  
 Arrigoni, Francesca I. F. 646  
 Aryal, Manish 193  
 Asafu-Agyei, Nana Akua 812  
 Asangbeh, Serra Lem. 1066  
 Ash, Samantha 735  
 Ashby, Rhonda 1055  
 Aslam, Maria V. 1083  
 Aslam, Samia 88, 570  
 Asmuth, David M. 205, 325, 502, 634  
 Asokan, Mangaiarkarasi 28, 357  
 Assaf, Ryan D. 975, 976  
 Assoumou, Lambert 867  
 Astemborski, Jacque 591, 883  
 Astorga Gamaza, Antonio 323, 329  
 Atim, Pamela 775  
 Atindaana, Edmond 372  
 Atkinson, Andrew 712  
 Attenborough, Teresa 809  
 Attia, Engi F. 811  
 Aubert, Vincent 246  
 Audsley, Jennifer 610, 613  
 Augustin, Max 335  
 Auld, Andrew F. 831  
 Auld, Sara C. 728  
 Aung, Khin Sanda 563  
 Aung, Su 1056  
 Avalos, Ava 505, 734  
 Avelino-Silva, Vivian I. 1012  
 Avendaño-Ortiz, Jose 247  
 Averitt, Dawn 2  
 Avery, Ann K. 1026  
 Avettand-Fenoel, Veronique 299, 804, 807, 828  
 Avihingsanon, Anchalee 599, 610, 613, 725, 808  
 Avila-Rios, Santiago 542, 876, 877  
 Avoundjian, Tigran 897  
 Aweeka, Francesca 52, 602  
 Awuah, Dominic 1061  
 Awuor, Merceline 1060  
 Axthelm, Michael K. 352  
 Ayers, Colby 648, 649  
 Ayieko, James 138, 668, 761, 1048  
 Ayles, Helen 92, 512, 833, 1079  
 Aza-Gnandji, Marlène 99  
 Aziz, Maliha 239, 240, 520  
 Azumah, Marilyn M. 1061  
 Azzoni, Livio 136, 304  
**-B-**  
 Baack, Brittney N 746  
 Baccarelli, Andrea A 332  
 Bacchetti, Peter 569  
 Bachmann, Nadine 400  
 Bachmann, Niklas 315  
 Bada, Florence 451  
 Badia, Roger 206  
 Badley, Andrew D 189, 295  
 Baeten, Jared 111, 127, 152, 707, 710  
 Baggaley, Rebecca 708  
 Bahemana, Emmanuel 519, 732  
 Bailin, Samuel 521, 522, 523, 531  
 Bailon, Lucia 161  
 Bain, Anthony R 500  
 Bain, William 116  
 Bainbridge, Veronica 126  
 Baisley, Kathy 524  
 Bakeera-Kitaka, Sabrina 175  
 Baker, Jason 492  
 Baker, Mark 373  
 Baker, Owen R 690  
 Baker, Phillip 201  
 Balachandra, Shirish 143  
 Balaji, Alexandria 656  
 Balakasi, Kelvin 181  
 Balakrishnan, Mini 425  
 Balazs, Alejandro 160, 263  
 Balderas, Robert 215  
 Baldini, Francesco 336  
 Bale, Michael J 304, 594  
 Ballana, Ester 206  
 Ballif, Marie 615  
 Bally, Alexander P 157  
 Balmert, Lauren C 590  
 Baltimore, David 160  
 Balyegisawa, Apolo 94  
 Balzer, Laura B 151  
 Bamford, Laura 409  
 Bancroft, Elizabeth A 758  
 Bandeem-Roche, Karen 140  
 Bang, Heejung 184  
 Banga, Riddhima 308  
 Bangdiwala, Ananta 131  
 Bansai-Matharu, Loveleen 507  
 Bao, Yajing 518  
 Bar, Katharine J 83, 123, 277, 296, 642  
 Baral, Stefan 669, 733, 735, 770  
 Baranovsky, Sergey 390  
 Barath, Justin 776  
 Barbee, Lindley 665  
 Barbera, Lauren K 546  
 Barbini, Birgit 540  
 Barco, Ambra 335  
 Bardiot, Dorothee 387  
 Bargalló, Manel E 228  
 Baric, Ralph 384, 618, 777  
 Baril, Jean-Guy 651  
 Barin, Francis 698  
 Barnabas, Ruanne 111, 123, 648, 755  
 Bärnighausen, Till 753  
 Barouch, Dan 123, 285, 717  
 Barr, Beth Tippett 635  
 Barr, Elizabeth 91  
 Barr, Liz 418  
 Barrett, Stephanie 88  
 Barrios, Rolando 628, 664  
 Barruz, Pilar 534  
 Bartels, Lina 485  
 Bartenschlager, Ralf 394  
 Barth, Thomas 213  
 Bartlett, Noah 646  
 Bartley, Christopher M 165  
 Bartolini, Niccolò 693  
 Barzon, Luisa 623, 624  
 Bass, Joseph 240  
 Bassett, Ingrid V 486, 563, 564, 769  
 Bassler, John 105  
 Basso, Monica 693  
 Bastarache, Lisa 626  
 Batey, David S 105  
 Battegay, Manuel 449, 450  
 Bauermeister, José A 706, 716, 723  
 Baugh, Bryan 403  
 Baugher, Amy 712  
 Baumgarten, Axel 442  
 Baxevanidi, Evangelia Eva 572  
 Baxter, Amy 303  
 Bayer, Cara 755  
 Bayoa, Florence 186  
 Beamner, May 147  
 Bearon, Rachel 365  
 Beauchamps, Laura 260  
 Beaumont, Kristin 302  
 Beck-Engeser, Gabriele B 98, 254  
 Becker, James 324, 338  
 Beckerman, Karen 584  
 Beddall, Margaret H 273  
 Bedimo, Roger 478  
 Bednash, Joseph 214  
 Beesham, Ivana 152  
 Beg, Subul 315  
 Begley, Rebecca 89, 375  
 Béguélin, Charles 449, 450, 452  
 Behel, Stephanie 143  
 Beigelman, Leonid 387  
 Bekerman, Elena 717  
 Bekker, Adrie 171, 605  
 Bekker, Linda-Gail 149  
 Beksinka, Mags 152  
 Belanger, Bruce 364  
 Belden, Andrew 323, 333, 672  
 Belkaid, Yasmine 237  
 Bell, Jennifer 222  
 Bellagamba, Rita 334  
 Bellet, Jonathan 419  
 Beltrao, Pedro 187  
 Belus, Jennifer M 400

- Ben Mechlia, Mohamed 148  
 Bena, Jason 730, 762  
 Benachi, Alexandra 582  
 Benade, Mariet 766  
 Bender Ignacio, Rachel A 239, 252, 543  
 Bender, Alexandra M 285  
 Bender, Melverta 105  
 Benfield, Thomas 499, 502, 532  
 Bengtson, Angela 574  
 Benjapornpong, Khunthalee 359  
 Benko, Erika 305  
 Benn, Paul 401, 402, 541  
 Bennett, Amy 644  
 Bennett, Kara 609  
 Benning, Lorie 539  
 Benson, Constance A 178  
 Benson, Paul 417  
 Berendam, Stella J 83, 296  
 Berenguer, Juan 441, 544, 549  
 Béréziat, Véronique 511  
 Berger, Alice 267  
 Berhanu, Ribka 134  
 Berhe, Mezgebe 127, 414  
 Berko, Jeff 110  
 Berman, Joan 322, 699  
 Berman, Leslie 181  
 Bermejo, Amanda 619  
 Bermejo, Mercedes 228  
 Bernard, Caitlin 743  
 Bernardino, Jose I 393, 453, 460, 534, 535  
 Bernardo, Edson 660  
 Bernasconi, Enos 449, 450, 457  
 Berrada, Stephanie 750  
 Berrie, Leigh 675  
 Berrocal, Leire L 641  
 Berry, Amanda 637  
 Bertholet, Nicolas 457  
 Bertoli, Ada 137  
 Best, Brookie 604, 607  
 Bester, Stephanie Marie 420  
 Betts, Michael 277, 282  
 Beyrer, Chris 735  
 Bhatt, Dhaval P 188  
 Bhatta, Manasa R 726  
 Bhondoekhan, Fiona 324  
 Bian, Aihua 726  
 Bibangambah, Prossy 495  
 Bickel, Markus 439, 442  
 Bien-Gund, Cedric 677  
 Bility, Moses T 200  
 Billong, Serge C 733  
 Birabaharan, Morgan 520  
 Biradar, Shivkumar 200  
 Bischoff, Jenny 455  
 Bishop, Marley 284  
 Bisson, Gregory P 559  
 Bitossi, Camilla 266  
 Bittencourt, Marcio Sommer 497  
 Bjorkman, Pamela J 115, 116  
 Blackard, Jason T 462  
 Blackmer, Jane Elizabeth 155, 309  
 Blain, Hubert 537  
 Blair, Paul 209  
 Blair, Wade 294, 717  
 Blanch-Lombarte, Oscar 210, 264, 265, 281  
 Blanco, Ignacio 265  
 Blanco, Jose L 641  
 Blanco, José-Ramón 527, 641  
 Blanco, Julià 226, 256, 259, 265  
 Blanford, Ann 753  
 Blankson, Joel 223, 275  
 Blas-García, Ana 453  
 Blatt, Lawrence M 387  
 Blaylock, Jason 483  
 Blinow, Andrew 390  
 Bloomfield, Gerald S 496, 498, 612  
 Blumenthal, Jill 711, 713  
 Bobardt, Michael D 381  
 Boccara, Franck 511  
 Boccuto, Adele 693  
 Bock, Peter 678, 680, 682  
 Boddapati, Arun 118  
 Boeck, Jordan 254  
 Boesecke, Christoph 439, 442, 455, 686  
 Boffito, Marta 393  
 Bogart, Laura M 769  
 Bogers, Susanne 391, 392  
 Bogorodskaya, Milana 497  
 Bogunovic, Dusan 388  
 Bohan, Dana 389  
 Bohlius, Julia 479, 485, 610  
 Boily, Marie-Claude 669, 708, 733, 735  
 Bolland, Sandro 387  
 Bole, Medhavi 665  
 Bollimpelli, Venkata Satish 583  
 Bolton, Carolyn 600  
 Boltz, Valerie F 116  
 Bolzenius, Jacob 333  
 Bondi, Mark W 327, 331  
 Bonfill, Eva 412  
 Bonnet, Fabrice 537  
 Bonora, Stefano 335  
 Bonvillian, Andrew 203  
 Booth, Michael 378  
 Booton, Ross D 669  
 Bordoni, Veronica 336  
 Borges, Alvaro H 532  
 Borges, Monica 673  
 Borisevich, Viktoriya 426  
 Boritz, Eli A 299, 304, 345  
 Borkird, Thitiporn 595  
 Borok, Margaret 169  
 Borowski, Luann 241  
 Borquez, Annick 772  
 Bortolami, Alessio 624  
 Bosch, Berend-Jan 385  
 Bosch, Ronald J 241, 311, 654  
 Bosch, Zama 133  
 Boschini, Antonio 242  
 Bosek, Everline 427  
 Bosinger, Steven 118  
 Bosse, Matthew 505  
 Boswell, Kristin L 117, 271  
 Botha, Johannes C 594  
 Bott, Matthew 169  
 Boucher, Charles AB 695  
 Boufassa, Faroudy 537  
 Bouhaddou, Mehdi 187  
 Boulware, David 131, 321  
 Bourgi, Kassem 509  
 Bousleiman, Stephanie 184  
 Boutron-Ruault, Marie-Christine 511  
 Bouzidi, Mohamed 234  
 Bowcock, Anne M 166  
 Bowman, Cindy Nicole 268  
 Bowman, Emily 214  
 Bowring, Anna 733  
 Box, Helen 379  
 Boyani, Saanjh 643  
 Boyd, Anders 452  
 Boyd, Cynthia 102  
 Boyd, Mary Adetinuke 759  
 Bradley, Chip 483  
 Bradley, Heather 636, 638  
 Brady, Kathleen 677  
 Brain, Danielle 379  
 Brainard, Diana 127, 220, 393, 395, 415, 430, 617  
 Brander, Christian 161, 264, 265  
 Branscome, Heather 249  
 Brar, Indira 629  
 Brassard, Nathalie 303  
 Brates, Irena 135  
 Braun, Dominique 425  
 Braunstein, Sarah L 765  
 Bread, Autumn 678, 682  
 Brechley, Jason 201, 240, 279  
 Brenner, Bluma G 651  
 Brew, Bruce 162, 551, 552  
 Brewster, L Madden 493  
 Brey, Zameer 134  
 Bricker, Katherine M 83, 204  
 Brickman, Adam M 332  
 Brijkumar, Jaysingh 95  
 Brindl, Niall 633  
 Brinson, Cynthia 220  
 Briz, Verónica 159  
 Broadwell, Carly 573  
 Brockman, Mark A 432  
 Brodin, Petter 172, 622  
 Brody, Steven L 188  
 Brooks, Alyssa 621  
 Brooks, Jennifer 484  
 Brooks, Kristina 366, 367  
 Brothers, Jennifer 366, 367  
 Brou, Hermann 186  
 Broussard, Janessa 730, 762  
 Brown, Helen 158  
 Brown, Jennifer A 400, 431  
 Brown, Lillian B 151, 627  
 Brown, Sheldon 478  
 Brown, Todd 322, 458, 503, 515, 518, 526, 536  
 Brown, Wendy 301  
 Browning, Renee 587, 605  
 Bruce, Andrew 111  
 Bruchez, Anna 215  
 Bruguera, Andreu 405  
 Brumme, Chanson 283, 432  
 Brumme, Zabrina L 283, 432  
 Brummel, Sean 176, 177, 587  
 Brunet, Cécile 570  
 Brunet, Laurence 406  
 Bryant, Kendall 97  
 Bryson, Bryan 461  
 Buchacz, Kate 102, 104, 504, 654, 752  
 Buchbinder, Susan P 730  
 Buckner, Clarisa 273  
 Budnik, Piotr 541  
 Budoff, Matthew 538  
 Buetikofer, Lukas 610  
 Bui, Eida 570  
 Bukasa, Laurette 586  
 Bukusi, Elizabeth A 151, 152, 635  
 Bunda, Bridget A 769  
 Bunge, Katherine 147  
 Bunglawala, Fazila Sadik 365, 374, 377, 378, 606  
 Buranapraditkun, Supanee 154, 359  
 Burchell, Ann N 484  
 Burchett, Chelsie 513  
 Burdick, Ryan C 79  
 Burdo, Tricia H 494, 496  
 Burgess, Jacqueline 747, 750  
 Burgi, Alina 705  
 Burgos-Gibrian, Joaquin 207, 306, 405  
 Burk, Robert 168  
 Burkholder, Greer 543  
 Burns, Charles 673, 773  
 Burns, David 718  
 Busakhala, Naftali 486  
 Busca Arenzana, Carmen 339, 441, 453, 460  
 Bushman, Lane 92, 366, 367  
 Buskin, Susan 644  
 Buta, Sofija 388  
 Butame, Seyram 744  
 Butler, Christopher C 754  
 Butt, Adeel 521  
 Buttery, Shannen 162  
 Buysman, Erin K 525  
 Buzko, Oleksandr 388  
 Buzón, Maria José 207, 269, 278, 300, 306, 386  
 Bwana, Mwebesa 95  
 Byakika-Kibwika, Pauline 368  
 Byakwaga, Helen 486  
 Byrareddy, Siddappa N 382  
 Byrne, Anthony 551, 552  
 Byrne, Kelly 175  
 Byrne, Morgan 533, 643  
 -C-  
 Cabello Úbeda, Alfonso 339  
 Cabello, Robinson 650  
 Cable, Russell 640  
 Cabrera, Cecilia 206  
 Cabrera-Rodríguez, Romina 226  
 Caceres, Carlos F 772  
 Cachay, Edward R 136, 410, 411, 456, 468, 542, 543  
 Cadiñanos, Julien 534, 535  
 Cagnot, Carole 537  
 Cai, Yanhui 220  
 Caicedo, Ana 413  
 Calabro, Valerie 385  
 Calantone, Nina 240  
 Calatayud, Laura 256  
 Calcagno, Andrea 335, 371  
 Cale, Evan M 160  
 Callebaut, Christian 128, 361, 425, 428, 717  
 Calmy, Alexandra L 343, 449, 450, 457  
 Calonge, Esther 228  
 Calvet-Mirabent, Marta 269  
 Calvez, Vincent 429  
 Calvi, Rachela 287  
 Calvino, Valeria 748  
 Calvo, Gino M 772  
 Calzada, Maria Jose 216  
 Calzado, Sonia 544  
 Cameron, Paul U 280  
 Camici, Marta 334  
 Campbell, Danielle 418  
 Campbell, Jonathon R 561  
 Campbell, Kayla 91  
 Campbell, Lucy 508, 540  
 Campbell, Thomas 169  
 Campione, Alexandra 643  
 Campioni, Paolo 336  
 Canestri, Ana 570  
 Caniglia, Ellen 571, 576  
 Cantarutti, Anna 623, 624  
 Cantero-Pérez, Jon 278  
 Cantos Lucio, Valeria D 547  
 Cantos, Anyelina 212, 332  
 Cantres, Yisel 350  
 Cao, Liwei 250  
 Cao, Yanguang 360  
 Cao, Youfang 87, 376  
 Capeau, Jacqueline 419, 511  
 Capobianchi, Maria Rosaria 336  
 Caperferri, Adam A 639  
 Capparelli, Edmund 605, 606, 607, 608, 609  
 Cappelletti, Giuseppina 137  
 Carabelli, Julieta 210, 281  
 Carbonari, Dena M 136  
 Carey, Jennifer 464  
 Carfi, Andrea 86, 618  
 Carlander, Christina 476  
 Carlander, Christina 487  
 Carlson, Kimberly J 504, 752  
 Carlucci, James G 614  
 Carmen María, Gonzalez-Domenech 445  
 Carmona, Francesco 623  
 Carmona, Sergio 689, 691  
 Carr, Michelle 653  
 Carrasco, Itziar 581, 597, 616  
 Carrasco-Hernandez, Rocío 251, 653  
 Carrasquillo, Jorge A 202  
 Carratala, Jordi 256  
 Carrico, Adam W 539  
 Carrico, Justin 704  
 Carrillo, Jorge 259, 265  
 Carroll, Constance 740  
 Cartwright, Emily Jeanne 454  
 Carvajal, Ana Eloisa 235

- Casado, Concepción 226  
 Casado, Jose L 641  
 Casanova, Jordi 405  
 Casazza, Joseph P 160, 193  
 Caskey, Marina 609  
 Casper, Corey 474  
 Cassim, Haseena 177  
 Castagna, Antonella 127, 393, 395, 748  
 Castel, Amanda 533  
 Castellon, Marvin 630  
 Castellví, Josep 278  
 Castellnuovo, Barbara 94  
 Castilho, Jessica L 726  
 Castillo-Mancilla, Jose R 92, 398  
 Castor, Delivette 554, 630  
 Castro-Álvarez, Juan Miguel 535  
 Cavalcante, Solange 556  
 Cavallari, Eugenio Nelson 470, 472  
 Cavassini, Matthias 97, 308, 343, 449, 450  
 Cazanave, Charles 537  
 Ceccarelli, Giancarlo 208, 470  
 Ceccherini-Silberstein, Francesca 137, 429, 748  
 Cedeño, Samandhy 161  
 Celani, Luigi 470  
 Cele, Sandile 263  
 Celentano, David C 447, 719, 737  
 Celum, Connie L 111, 563, 564  
 Centeno-Mediavilla, Cristina 278  
 Cerrillo, Ildelfonso Sanchez 216, 269  
 Cerutti, Gabriele 85  
 Cervero, Miguel 159  
 Cesarman, Ethel 169  
 Cha, Susan 712  
 Chabrol, Amélie 570  
 Chadwick, Ellen Gould 573, 575  
 Chagaris, Kalliope 752  
 Chahin Anania, Carolina 416  
 Chahroudi, Ann 83, 204, 296, 621  
 Chaila, Mwate Joseph 477, 679  
 Chaillon, Antoine 248, 274, 288, 440, 632, 652, 692  
 Chaisson, Lelia H 556  
 Chaisson, Richard E 130, 178  
 Chaiyahong, Prachya 370  
 Chakhtoura, Nahida 177  
 Chaltin, Patrick 387  
 Chambrin, Véronique 570  
 Chamie, Gabriel 151  
 Chamudzi, Mishek 491  
 Chamorro, Anna 259, 265  
 Chan, Courtney 473  
 Chan, Kun-Wei 250  
 Chan, Owen 238  
 Chan, Philip 700  
 Chan, Phillip 323, 340  
 Chan, Sarah-Marie 110  
 Chanaiwa, Vongai Margaret 569  
 Chanda, Duncan 759  
 Chandak, Aastha 397  
 Chandler, Geetanjali 734  
 Chandiwana, Nomathemba 517, 572  
 Chandrashekar, Abishek 717  
 Chang, David 519  
 Chang, Hsien-Yen T 700  
 Chang, Jennifer 630  
 Chang, Jonathan L 495  
 Chang, Joy C 435, 761  
 Chang, Judy 280  
 Chang, Mindy 637  
 Chang, Silvia 430  
 Chang, Stephanie 169  
 Chang, Sui-Yuan 463, 465  
 Chang, Weizhong 195  
 Chantaratin, Sasitorn 601  
 Chapin-Bardales, Johanna 712  
 Chappell, Catherine Anne 368  
 Chariyalertsak, Suwat 716  
 Charlebois, Edwin D 151  
 Charlebois, Roxanne 303  
 Charles, Benedict 184  
 Charlotte, Frédéric 511  
 Charlton, Bethany 262  
 Charpentier, Charlotte 404, 429  
 Chasela, Charles 182  
 Chassiakos, Alexander John 273  
 Chattergoon, Michael 217  
 Chatterjee, Debashree 233  
 Chaudhary, Omkar 244, 483  
 Chauma-Mwale, Anne 634, 746  
 Chavis, Lee 346  
 Chawana, Tariro Dianah 567  
 Chawarski, Marek C 683  
 Cheerdarla, Narayana 583  
 Cheinquer, Nelson 135  
 Chemtai, Linda 486  
 Chen, Athena 275  
 Chen, Benjamin K 302, 342  
 Chen, Grace Q 430  
 Chen, Guan-Jhou 465  
 Chen, Janet S 617  
 Chen, Kuo-Chan 123  
 Chen, Peter 122  
 Chen, Qian 195  
 Chen, Tao 175  
 Chen, Ying Q 580  
 Cheney, Carol 316  
 Cheng, Chih-Ning 132  
 Cheng, Matthew P 372  
 Cheng, Shu-Hsing 414  
 Cheng, Yu 338  
 Cherepanov, Peter 120  
 Chettimada, Sukrutha 320  
 Cheung, Hoi Ching 185  
 Cheung, Peter K 432  
 Chevalier, Joshua M 309  
 Chew, Kara W 396, 555  
 Chi, Benjamin 647  
 Chiao, Elizabeth 471  
 Chiarella, Jennifer 287, 751  
 Chiasson, Mary Ann 706  
 Chibesa, Linda Mwila 477, 679  
 Chimbetete, Cleophas 615  
 Chinula, Lameck 176, 177, 587  
 Chipato, Tsungai 567, 569  
 Chirwa, Lameck 759  
 Chiu, Chris Y H 280  
 Chlanda, Petr 394  
 Cho, Kyu 672  
 Cho, Yong Soon 370  
 Chohan, Bhavna 427, 566, 721  
 Chohan, Bhavna 577, 722  
 Choi, Mary 513  
 Chokephaibulkit, Kulkanya 601  
 Chokkalingam, Anand P 393, 395  
 Chomchey, Nitiya 179, 340, 407  
 Chomont, Nicolas 154, 280, 289, 298, 301, 303, 359, 595  
 Chottanapund, Suthat 359  
 Chounta, Vasilki 402  
 Chow, Dominic C 238  
 Chow, Felicia C 98  
 Chow, Ryan 165  
 Christ, Benedikt 615  
 Christensen, Stefan 439, 442  
 Christopoulos, Katerina 409, 410, 411, 762  
 Christy, Lavine Lynn 276  
 Chu, Helen Y 261  
 Chu, Xiuping 318, 483  
 Chuang, Yu-Chung 132, 463, 465  
 Chun, Tae-Wook 299, 309  
 Chung, Michael H 611  
 Ciaranello, Andrea 150, 568  
 Ciardi, Antonio 470  
 Cicalini, Stefania 334, 545  
 Cihlar, Tomas 294, 717  
 Cimbro, Raffaello 236  
 Cimini, Eleonora 242, 336  
 Ciocca, Emily T 464  
 Clark, Jesse 221, 530  
 Clark, Meredith 715  
 Clark, Sabrina 341  
 Clarke, Amanda 508  
 Clarke, Diana F 607  
 Clarke, William 678, 682, 690  
 Clement, Meredith Edwards 773  
 Clements, Janice 322  
 Clerc, Isabelle 229  
 Clifford, David 101  
 Climent, Nuria 412  
 Clipman, Steven J 694  
 Cloete, Allandise 657  
 Clotet, Bonaventura 161, 206, 210, 259, 264, 265, 281  
 Clough, Erin 346  
 Clutton, Lucy 756  
 Cluver, Cathy A 171  
 Cluver, Lucie 589  
 Coates, Emily E 608  
 Coates, Thomas J 149  
 Cobey, Sarah E 694  
 Coburn, Bryan 372  
 Cockett, Mark 421, 422  
 Coelho, Lara 153, 510  
 Coetzee, Heather 742  
 Coffin, John M 255, 304, 639  
 Cofrancesco, Joseph 223  
 Cohen, Craig 151, 635  
 Cohen, Eric A 267  
 Cohen, Susan E 539  
 Cohen, Myron S 121, 123, 150, 153, 580, 718  
 Cohn, Silvia 556  
 Cohn, Susan E 91  
 Coiras, Mayte 159  
 Colasanti, Jonathan 104, 547, 654  
 Colbers, Angela 175  
 Colby, Donn J 179, 340, 407, 408, 672  
 Cole, Basiel 215  
 Cole, Stephen 578  
 Coleman, Charl 640  
 Coleman, Stacey 92  
 Coletti, Anne 176  
 Colie, Christine 168  
 Colin, Andrew 611  
 Coll, Pep 161  
 Collazo-Rodriguez, Bryan J 350  
 Collens, Sarah Isabel 307  
 Collier, Ann C 101  
 Collins, Lauren F 526, 547  
 Collins, Sean E 369, 415, 425, 430  
 Collora, Jack A 287  
 Concato, Carlo 172, 622  
 Conce Alberto, Winiffer D 305  
 Conceição, Carolina M 205  
 Condrey, Jillian 297  
 Conell, Lucy 134  
 Connelly, Marge 324  
 Conner, Madelyn 578, 579  
 Connick, Elizabeth 276, 493, 500  
 Connolly, Stephen P 742  
 Conradie, Francesca 562  
 Conroy, Andrea L 592  
 Conway, Samuel 550  
 Conzelmann, Carina 213  
 Cook, Nicola J 120  
 Cooley, Sarah 164, 317, 319  
 Coombs, Robert 311, 555, 777  
 Cooper, Curtis 448, 484  
 Cooper, Emily 218  
 Corado, Katya 711, 713  
 Corball, Lucia 767  
 Corbett, Kizzmekia 618  
 Cordeiro-Santos, Marcelo 556  
 Corey, Lawrence 257, 718  
 Corley, Micheal 528  
 Cormack, Ian 684  
 Corma-Gomez, Anais 224, 466, 469  
 Cornelius, Amber M 119  
 Cornell, Morna 615, 662  
 Corpataux, Jean-Marc 308  
 Correll, Todd A 416  
 Cosma, Chiara 624  
 Cossarini, Francesca 115, 211, 219  
 Costagliola, Dominique 148, 511  
 Costenaro, Paola 623, 624  
 Cotter, Aoife G 96, 100, 231, 258, 742  
 Cotterchio, Michelle 484  
 Cotton, Mark F 594, 605  
 Cottrell, Mackenzie L 203, 204, 362, 363  
 Cottura, Nicolas 365, 374, 377, 378, 606  
 Cotugno, Nicola 172, 245, 246, 286, 598, 622  
 Coughlin, Jennifer 322  
 Council, Olivia D 344  
 Coupland, Helen 708  
 Cowan, Ethan 683  
 Cowen, Maria 249  
 Cox, Andrea 461  
 Cox, Joseph 448, 776  
 Cox, Stephanie 428  
 Coyle, Ryan 92  
 Cozzani, Sandra 624  
 Cozzi-Lepri, Alessandro 748  
 Crabtree Ramirez, Brenda 510, 565  
 Craig, Maryellen 298  
 Crane, Heidi 98, 104, 409, 468, 543, 654, 671  
 Cranmer, Lisa 558  
 Crauwels, Herta 403  
 Crawford, Jessica N 603  
 Crawford, Katharine HD 261  
 Crawley, Addie 699  
 Crear, Danita 105  
 Creed, Maria 742  
 Cremieux, Etienne 184  
 Crepez, Nicole 656, 760  
 Cramer, Manuel 227  
 Crespo, Marta 206  
 Cressley, Tim R 352, 353, 355, 444, 605  
 Creswell, Fiona 131  
 Cromarty, Ben 540  
 Crompton, Thomas 764  
 Cronin, Colm 742  
 Crook, Angela M 562  
 Cross, Robert W 426  
 Crothers, Kristina 478, 611  
 Crouch, Pierre-Cedric 762  
 Crowell, Trevor A 407, 519, 732  
 Cruz, Michael 219  
 Cuadros, Diego 524, 648  
 Cucurull, Josep 641  
 Cui, Zishan 776  
 Cummings, Derek A T 694  
 Cummings, Nathan W 189, 295, 380  
 Cunningham, Coleen K 608  
 Cunningham, Philip 551  
 Curanovic, Dusica 324  
 Curley, Paul 379  
 Curran, Adria 306, 412  
 Curran, Kathryn 688  
 Currier, Judith S 176, 177, 396, 494, 496, 555  
 Curtis, Alan D 618  
 Cyskter, Joshua 241  
 Cysique, Lucette A 162, 551, 552  
 -D-  
 Da Dalt, Liviana 624  
 Da Silva Castanha, Priscila 116  
 Da Silva, Juliana 761  
 Daama, Alex 720, 763  
 Daar, Eric S 396, 555  
 Dadabhai, Sufia 587  
 Daeppen, Jean-Bernard 457  
 Daeumer, Martin 442  
 Dahourou, Désiré Lucien 614  
 Dai, Weiwei 293, 315  
 Dakhia, Samia 402  
 Dale, Helen 143  
 Dallas, Ronald 603  
 Dalmau, David 405, 527  
 Dalmau, Judith 281  
 Daly, Michele B 297  
 Damas, José 343  
 D'Amico, Ronald 402, 505, 541  
 Damra, Mohammad 114, 156  
 Dandekar, Ravi 165  
 Daniels, Christine Nicole 268  
 Dantanarayana, Ashanti 280, 301  
 D'Antoni, Michelle L 438  
 Dapp, Michael 284  
 D'Aquila, Richard T 221, 229, 240  
 Darko, Sam 192, 193  
 Darley, David 551, 552  
 Darling, Katharine E A 343, 457  
 D'Arminio Monforte, Antonella 748  
 Das, Moupali 428  
 Dasgupta, Sayan 252  
 Daud, Ibrahim 612  
 Davenport, Miles P 277  
 Davidović, Maša 479, 485  
 Davies, Mary-Ann 615, 662  
 D'Avolio, Antonio 371  
 Davy-Mendez, Thibaut 410, 411  
 Dawson, Keith M 385

- Dawson, Rodney 130  
 De Clercq, Jozefien 215  
 De Freitas, Marcelo Araujo 741  
 De Girolamo, Gabriella 470  
 De La Fuente, Hortensia 216  
 De La Fuente, Sara 339  
 De La Grecca, Robert 257, 718  
 De León Luis, Juan Antonio 581  
 De Los Santos, Ignacio 216, 269, 469  
 De Miguel, Marta 441  
 De Miguel, Rosa 534, 535  
 De Montigny, Lina 604  
 De Nicolò, Amedeo 371  
 de Oliveira, Tulio 263  
 De Pablo, Rocio M 235  
 De Paris, Kristina 579, 618  
 De Rossi, Anita 172, 596, 622, 623, 624  
 de Souza, Mark 179, 595  
 De Truchis, Pierre 419  
 De Vivo, Elisa 371  
 De Voux, Lucien 764  
 De Waal, Leon 385  
 De Waard, Liesl 171  
 De Witte, Lotje 342  
 De Zottis, Federico 334  
 Dean, Gary E 462  
 Dean, Lorraine T 700  
 Dear, Nicole 519, 732  
 Decloedt, Eric 605  
 Dee, Anindya 143  
 Deeks, Steven Grant 220, 254, 275, 289, 298, 301, 304, 311, 312  
 Deese, Jen 152  
 Defechereux, Patricia 762  
 Degrange, Paula 202, 203  
 DeGrosky, Michelle 126  
 Deikus, Gintaras 305  
 Deitchman, Amelia N 254  
 DeJesus, Edwin 127, 220  
 Del Duca, Giulia 334  
 Del Rio Estrada, Perla Mariana 273  
 Del Romero-Raposo, Jorge 544  
 Del Vecchio, Natascha 653  
 Delaney, Joseph A C 98, 409, 468, 543  
 Delaney, Kevin P 739  
 Delaugerre, Constance 148  
 DeLaurentis, Clare 554  
 deLazzari, Elisa L 641  
 Deleage, Claire 203, 236, 271  
 Dele-Oni, Ruth 437  
 Delgado, Cristina 269  
 Delgado, Gloria Gabrielle 303  
 Delgado, Jesus 169  
 Delgado-Hierro, Ana 544  
 Dellicour, Simon 632  
 Delobel, Pierre 537  
 Delorenzi, Mauro 308  
 DeMarino, Catherine 249  
 Demberg, Thorsten 214  
 Demonde, Sophie 614  
 Dempsey, Suzanne 742  
 Deng, Xutao 310  
 Denkinger, Claudia 633  
 Dennehy, Michelle K 709  
 Denny, Thomas 116  
 Denti, Paolo 90  
 Derfuss, Tobias 343  
 DeRisi, Joseph 165  
 Derry, Heather 513  
 Desai, Jui 685  
 Desai, Seema 247  
 Descamps, Diane 404, 429  
 Deschamps, Marie Marcelle 185  
 Deshpande, Vijeta 771  
 DeSouza, Christopher A 493, 500  
 DeSouza, Noah M 493  
 Desrosiers, Ronald C 270  
 Dessie, Melaku 646  
 Dettinger, Julia 707, 710  
 D'Ettorre, Gabriella 208, 470, 472  
 Deus, Maria 173  
 Deval, Jerome 387  
 Devieux, Jessy 184  
 DeVos, Joshua R 435, 761  
 Dhairyawan, Rageshri 727  
 Dhakal, Sushil 389  
 Dhanireddy, Shireesha 665  
 Dhillon, Nalin 664  
 Dhokotera, Tafadzwa G 479, 485  
 Di Chiara, Costanza 623, 624  
 Di Germanio, Clara 310  
 Di Mascio, Michele 202, 203  
 Di Nunzio, Francesca 78  
 Di Perri, Giovanni 335, 371  
 Di Salvo, Giovanni 624  
 Diacon, Andreas 562  
 Diallo, Karidia 675  
 Diamond, Tracy Lauren 129, 376  
 Dias, Danilo 313  
 Dias, Joana 82  
 Diaz De Santiago, Alberto 339  
 Diaz Tsuzuki, Manami 762  
 Diaz, Ricardo S 313  
 Diaz, Sharmin 230  
 Diaz-Cuervo, Helena 393, 406, 503  
 Dicker, Ira B 421  
 Diero, Lameck 509  
 Dietze, Kenneth 595  
 Díez, Cristina 544, 549  
 Díez-Fuertes, Francisco 228  
 Dillner, Joakim 476  
 Dillon, Stephanie 218  
 Dimitrov, Dobromir 669, 733, 735  
 Ding, Lingmei 80, 196  
 Ding, Shilei 86  
 Dinh, Chuong 297, 714, 715  
 Dinh, Vinh B 245, 246, 286  
 DiPerna, Alexandra 575  
 Dirajjal-Fargo, Saheera 613  
 Diseko, Modiegi 571, 576, 588  
 Dobard, Charles 714  
 Dobra, Adrian 753  
 D'Offizi, Gianpiero 545  
 Doi, Naoko 181  
 Dolezal, Curtis 398  
 Dombrowski, Julia C 644, 665  
 Domingo, Pere 126, 405, 412, 413, 441  
 Dominguez Islas, Clara 147  
 Dominguez, Kenneth L 106, 701  
 Dominguez, Lourdes 441  
 Dominguez-Rodriguez, Sara 581, 596, 619, 620  
 Donà, Daniele 172, 622, 623, 624  
 Doncel, Gustavo 715, 716  
 Dong, Winnie K 432  
 Dong, Xueyuan 106, 656, 687, 760  
 DONG, Yongquan 471  
 Donnell, Deborah 152, 580, 669, 678, 680, 682  
 Donnelly, Ryan 377  
 D'Onofrio, Gail 683  
 Donovan, John 777  
 Dooley, Kelly 90  
 Doores, Katie J 120  
 Doran, Peter 96, 258  
 Dore, Greg 551, 552  
 Doria-Rose, Nicole 273  
 Dorman, Susan 130  
 Dorosh, Michael Jon 418  
 Dorrell, Lucy 262  
 Dorsey, Kerri 643, 724  
 Dorvil, Nancy 184, 185  
 Dorward, Jienchi 754  
 Doshi, Jalpa A 700  
 Doshi, Rupali K 643, 724  
 Dossani, Zain Y 234, 310  
 Dossantos, Sandy 352, 353  
 Douek, Daniel C 82, 192, 193, 279  
 Dougan, Michael 122  
 Douglas, Pamela S 494, 496, 498, 506  
 Dovel, Kathryn 181  
 Dowdy, David 668, 775  
 Downing, Martin 706  
 Doyle, Margaret 523  
 Dragoni, Filippo 693  
 Drain, Paul K 352, 353, 355, 563, 564, 661  
 Drake, Alison L 566, 577, 674  
 Drammeh, Bakary 143  
 Dramowski, Angela 171  
 Dreier, Birgit 85  
 Dretler, Robin H 414  
 D'Souza, Gypsamber 104, 168, 538, 626  
 Du Toit, Nicolene 171  
 Du, Li 234  
 Dubé, Mathieu 303  
 Duchon, Alice 190  
 Dudoit, Yasmine 511  
 Duerr, Ann C 239, 252, 284, 287, 650  
 Duff, Emma 732  
 Dufour, Caroline 303  
 Duggal, Priya 459  
 Dumond, Julie B 363  
 Dumont, Emelyne 184  
 Dumrongpisutikul, Netsiri 163  
 Dunham, Richard M 204  
 Dunlap, Amanda R 603  
 Du-Pasquier, Renaud 343  
 Duprez, Daniel 492  
 Durand, Christine 467  
 Durham, Marcus 504  
 Durieux, Jared C 490, 501  
 Durovni, Betina 556  
 Dvory-Sobol, Hadas 89, 127  
 Dweep, Harsh 114  
 Dyar, Christina 666  
 Dzabic, Mensur 476  
 -E-  
 Easterbrook, Philippa 444, 446  
 Eaton, Ellen F 410, 411  
 Eaton, Jeffrey 669  
 Ebert, Jessica A 436  
 Ebrahim, Ismael 371  
 Edelman, Jennifer E 683  
 Edlfsen, Paul T 239  
 Edmonds, Andrew 614  
 Edupuganti, Sripatha 718  
 Edward, Joshua 709  
 Edward, Vinodh 152  
 Edwards, Darin 618  
 Edwards, Jessie 109  
 Edwards, Robert 268  
 Efthimiou, Orestis 485, 662  
 Egger, Matthias 139, 479, 485, 610, 615  
 Egorova, Alina 390  
 Einkauf, Kevin B 155, 309  
 Eklund, Carina 476  
 Ekwe, Irene 167, 480  
 El Kamari, Vanessa 329  
 El Moussaoui, Rachida 695  
 El Sahly, Hana M 464  
 Elboudwarej, Emon 395  
 Elefante, Julius 663  
 Elion, Richard 503  
 Ellenberg, Susan S 642  
 Eller, Leigh A 275, 557  
 Elliott, Emilie 505  
 Elliott, Alison 131  
 Elliott, Jennifer L 188  
 Ellis, Ronald J 101, 325, 326, 328, 348, 667  
 Ellis, Shanon 146, 714  
 Ellison, Lucas 92, 366, 367  
 El-Nahal, Walid 734  
 Elorrea, Oliver A 772  
 El-Sadr, Wafaa M 186  
 El-Sayed, Manal H 444  
 Else, Laura 358, 361  
 Elser, Samra 199  
 Elson, Joanna L 325  
 Emerman, Michael 81, 292  
 Emerson, Brian 739  
 Emu, Brinda 244, 481, 483  
 Endress, Daniel 583  
 Engler, Olivier 385  
 Ennis, Nicole 744  
 Enugu, Ajay K R 145, 745  
 Epalza, Cristina 620  
 Erasmus, Kobie 171  
 Erem, Geoffrey 497  
 Erickson, James 249  
 Erlandson, Kristine 498, 518, 546, 667  
 Eron, Joseph J 241, 304, 396, 410, 411, 416, 555, 777  
 Ershov, Dmitry 78  
 Erti, Allison 656  
 Esber, Allahna 519, 557, 732  
 Escudero, Jaclyn 558  
 Eshleman, Susan 153, 275, 678, 680, 682  
 Eskander, Sherry 611  
 Esmailzadeh, Elmira 276  
 Espluges, Juan V 453  
 Esposito, Anthony M 302  
 Essajee, Shaffiq 568  
 Esteban-Cantos, Andrés 534, 535  
 Estes, Jacob 118  
 Estévez-Herrera, Judith 226  
 Etemad, Behzad 276, 437  
 Evans, Vanessa 280, 301  
 Evering, Teresa 253  
 Everitt, Daniel 562  
 Eves, Karen A 416  
 -F-  
 Fabeni, Lavinia 137  
 Fackler, Oliver T 394  
 Fahimi, Mansour 636, 638  
 Faith, Jeremiah J 219  
 Fajemisin, Wole 736, 774  
 Falcó, Anna 207  
 Falcó, Vicenç 207, 278, 306, 386, 405, 412  
 Falconer, Debbie 550  
 Falconer, Karolin 452  
 Fan, Run 531  
 Fanciulli, Chiara 441  
 Fancourt, Craig 376  
 Fandl, Hannah K 493  
 Fang, Lei 777  
 Fares, Mohamed 394  
 Farhadian, Shelli F 165, 751  
 Farias, Guilherme B 205  
 Farid, Samar 444  
 Farid, Shiza 674  
 Farnham, Paul 704  
 Farrell, Jeremy 742  
 Farzan, Michael 270  
 Fassati, Ariberto 233  
 Fatoye, Segun Kunle 736, 774  
 Fatti, Geoffrey 182, 766  
 Fauci, Anthony S 86, 236, 271  
 Faustin, Mikerlyne 184  
 Feeney, Eoin 96, 231, 258  
 Felizarta, Franco B 126  
 Fellay, Jacques 224  
 Felsen, Uriel R 765  
 Felton, Abby 81  
 Feng, Meizhen 129  
 Fenwick, Craig 308  
 Ferguson, Jane 531  
 Fernandez, Danielle 738  
 Fernandez, Reinaldo 680, 681  
 Fernandez-Fuertes, Marta 445, 466  
 Fernández-Luis, Sheila 660  
 Ferraris, Christopher 398  
 Ferreira, Edna 322  
 Ferrenberg, James 474  
 Ferrer, Josh 144  
 Feyzmezhad, Roya 250  
 Fichtenbaum, Carl 494, 496, 498, 506  
 Fidler, Sarah 142, 158, 678, 680, 682  
 Fields, Adam J 326  
 Fiellin, David A 454, 683  
 Fierer, Daniel 440  
 Figg, William D 167  
 Figueroa, Alexis 217  
 Figueroa-Romero, Antía 660  
 Filippidis, Paraskevas 343  
 Finkenflügel, Renee N N 695  
 Finzi, Andrés 86  
 Fiona, Burns 262, 508, 727  
 Firmhaber, Cindy S 493, 500  
 Fischer, William 777  
 Fischl, Margaret 247  
 Fisher, Azetta 574  
 Fisher, Katie 314  
 Fisher-Pearson, Natasha 262  
 Fitch, Kathleen 496, 498, 506  
 Fitzgerald, Daniel 180  
 Fitzgerald, Wendy 227  
 Flamm, Jason 97, 330  
 Fletcher, Courtney V 359, 368  
 Flexner, Charles W 379  
 Florence, Lot 698  
 Flores, Sonia 772  
 Flowers, Lisa 168

- Flynn, Jacob 201  
 Flynn, Patricia 587  
 Fogel, Jessica 153  
 Fojo, Anthony Todd 668, 734, 775  
 Foldyna, Borek 494  
 Fontillón, María 235  
 Forbici, Federica 336  
 Force, Lluís 412  
 Ford, Susan L 373, 402, 541  
 Forgie, Sarah 592  
 Foster, Caroline 596  
 Fouda, Genevieve 83, 296, 625  
 Foulds, Kathryn E 271  
 Foulkes, Caio 85  
 Fourati, Slim 82  
 Fowke, Keith 267  
 Fowler, Mary G 567, 587  
 Fowler, Rob 372  
 Fox, Julie 361, 508  
 France, Anne Marie 688  
 France, Michael 579  
 Franceschini, Nora 103, 141  
 Francesco, Bonfante 172, 622, 623, 624  
 Francis, Kate 586  
 Franco, Ricardo 456  
 Francoeur, Nancy 305  
 Francois, Eli Maxime 185  
 Frange, Pierre-Henri 570  
 Frank, Ian 723  
 Franklin, Donald 101  
 Frasca, Federica 208, 266, 472  
 Frater, John 158  
 Fray, Emily J 285  
 Freed, Eric O 424  
 Freedberg, Kenneth 150, 670, 771  
 Freeman, Bethany 578  
 Freeman, Esther 486  
 Freeman, Gordon J 157  
 Freeman, Jincong 712  
 Freeman, Michael L 227  
 Freiberg, Matthew 99, 232, 521, 523  
 French, Evan 103  
 Frenkel, Lisa M 239, 474  
 Friedrich, Nikolas 85  
 Frieze, Julia 761  
 Fromentin, Rémi 154, 280, 298, 303  
 Fu, Martina 140  
 Fuchs, Andreas Ejstrup 499  
 Fuchs, James 420  
 Fuchs, Sebastian P 270  
 Fuentes, Ana 466  
 Fuente-Soro, Laura 660  
 Fuhrer, Jack 504, 752  
 Fujimoto, Kayo 653  
 Fulcher, Jennifer A 221  
 Fullmer, Brandie 408  
 Fumadó, Victoria 620  
 Funderburg, Nicholas 214, 530  
 Furrer, Hansjakob 457  
 Fursa, Olga 443  
 Fusco, Gregory P 406  
 Fusco, Jennifer S 406  
 Fwoloshi, Sombó 759
- G-**  
 Gabitzsch, Elizabeth R 272  
 Gabra, Hani 389  
 Gabriel, Curtis Lee 531  
 Gabriel, Janelle 214  
 Gabuzda, Dana 320  
 Gagliardini, Roberta 242, 545  
 Gaisa, Michael M 166, 473  
 Galagan, Sean 563, 564, 661  
 Gale, Michael 84  
 Galindo, Frances 243  
 Galindo, Maria José 527  
 Galinskis, Juliana 13  
 Galiwango, Ronald 681, 690  
 Gallardo, Christian M 434  
 Gallay, Philippe 381  
 Galloway, Jared 261  
 Gallucci, Lara 394  
 Gálvez, Cristina 300  
 Gama, Lucio 82, 608, 609  
 Gandhi, Monica 289, 354, 355, 357, 569, 627, 699, 710  
 Gandhi, Rajesh Tim 95, 241, 304, 311  
 Ganesan, Anuradha 222, 318, 483  
 Ganesh, Aylur Kailasam 745  
 Gange, Stephen 247, 671  
 Gangireddy, Srushti 626  
 Ganoza, Carmela 287  
 Gant, Zanetta 656  
 Gantner, Pierre 154  
 Ganz, Peter 99  
 Gao, Ce 155, 225, 286, 307, 309, 437, 598  
 Gao, Hongmei 583, 618  
 Gao, Michael 773  
 Garai, Jillian 144  
 Garban, Hermes 272  
 Garber, David A 146  
 Garcia, Federico 466  
 García, Felipe 228  
 García-Broncano, Pilar 286  
 García-Cremades, Maria 561  
 García-Fraile, Lucio Jesús F 269, 544, 549  
 García-Leon, Alejandro 100, 258, 491  
 García-Lerma, Gerardo 297, 714, 715  
 García-Mesa, Yoelvis 347  
 García-Morales, Claudia 251  
 García-Pérez, Javier 386  
 García-Sastre, Adolfo 187, 211  
 García-Vidal, Benito 358  
 García-Vidal, Edurne 206  
 Gardner, Edward M 546  
 Gardner, Matthew R 270  
 Garetta, Dickman 648  
 Garibaldi, Brian 140  
 Garliss, Caroline C 223  
 Garrett, Meghan 261  
 Garrett, Nigel 754  
 Garrido, Carolina 618, 625  
 Gartland, Margaret 422  
 Gartland, Martin 421  
 Garvie, Patricia A 593  
 Garza, Rolando 347  
 Gasca-Capote, María C 194, 224  
 Gate, Kelly 754  
 Gatechompol, Sivaporn 91, 370  
 Gates, Thomas 162  
 Gatti, Francesca 693  
 Gaudinski, Martin R 117, 608, 718  
 Gaufin, Thaidra 542  
 Gaur, Aditya 603  
 Gausdal, Gro 389  
 Gayle, Julie 397  
 Gazy, Inbal 263  
 Gea-Mallorqui, Ester 262  
 Gebo, Kelly 102, 104, 671, 734  
 Geffner, Mitchell E 590, 613  
 Geidelberg, Lily 733, 735  
 Geisbert, Thomas W 426  
 Gelaude, Deborah 706  
 Geldmacher, Christof 557  
 Geleziunas, Romas 312, 425, 717  
 Gelman, Benjamin B 101, 344  
 Gelpi, Marco 499  
 Genade, Leisha 134  
 Genebat, Miguel 235  
 Genescà, Meritxell 207, 278, 306, 386  
 Genovese, Caitlyn 169  
 George, Gavin 95  
 George, Jomy 167, 475, 480  
 Gerace, Lucas 102, 670  
 Gerena, Yamil 350  
 Gerlo, Sarah 215  
 German, Polina 89, 369, 375  
 Gerschenson, Mariana 521, 590  
 Gerstoft, Jan 499, 502, 532  
 Gervassi, Ana 239  
 Geurts van Kessel, Corine H 124, 391, 392  
 Gharbharan, Arvind 124, 391, 392  
 Ghneim, Khader 84  
 Ghosh, Subash 145, 745  
 Ghoshhajra, Brian 495, 497  
 Ghosn, Jade 148  
 Gianella, Sara 248, 288, 348, 528, 529, 692  
 Giaquinto, Carlo 172, 596, 622, 623, 624  
 Gibowski, Severine 419  
 Gibson, Theda 621  
 Gijón, Manuel 619  
 Gill, Alexander J 347  
 Gill, M John 136, 456  
 Gilliland, Mac 357  
 Gillis, Jennifer 484  
 Gilsanz, Paola 330  
 Gilson, Richard 727  
 Ginsberg, Mindy S 765  
 Girardi, Enrico 242, 545, 748  
 Girdwood, Sarah Joy 691  
 Girod, Candace 656  
 Giron, Leila B 114, 156, 313, 458  
 Gisolf, Elisabeth H 695  
 Gisslen, Magnus 349  
 Gladkov, Gregory Takashi 309  
 Glass, Tracy 568  
 Glass, Tracy Renée 400  
 Glatt, Tanya 640  
 Glenny, Carrie 366, 367  
 Glesby, Marshall J 513  
 Glick, Sara 665  
 Glidden, Dave 354, 355, 627  
 Glögl, Matthias 85  
 Go, Young-Mi 512  
 Godbole, Sheela V 580  
 Godfrey, Catherine 91, 519, 738  
 Godinho-Santos, Ana 205  
 Goecker, Erin 777  
 Goedel, William C 700  
 Goetz, Jay 428  
 Goetz, Matthew 478, 521  
 Golden, Matthew R 644, 665  
 Goldfarb, Dennis 188  
 Goldman, Aaron R 114, 156  
 Goldstein, Harris 699  
 Goldstein, Rachel 736, 774  
 Goldstein, Zil 107  
 Golub, Jonathan 133, 556  
 Gomba, Yolanda 183  
 Gomez Lorenzo, Margarita M 718  
 Gomez, Gabriela 767  
 Gomez, Laurén 707, 710  
 Gómez-Ayerbe, Cristina 413, 445  
 Gomez-Mateos, Jesus 445  
 Goncalves, Priscila 167  
 Gong, Jingjing 238  
 Gonzales, Pedro 716  
 Gonzalez, Isidoro 216  
 Gonzalez, Marcos 388  
 González-García, Juan 441, 453, 460, 544, 549  
 Gonzalez-Perez, Antonio 224  
 Gonzalez-Reiche, Ana 211  
 Gonzalez-Serna, Alejandro 224, 445, 466  
 Good, Steven S 364  
 Goodey, Adrian 88  
 Goodkin, Karl 667  
 Goodwin, Lynsey C 142  
 Goolsby, Rachel 603  
 Gorbach, Pamina M 149, 221  
 Gordon, David E 187  
 Gordon, Kirsha 626  
 Gorelick, Robert 255, 408  
 Górgolas, Miguel 339  
 Gori, Andrea 748  
 Gorman, Jason 85  
 Gosnell, Bernadette 263, 563, 564, 661  
 Goswami, Suranjana 195  
 Goswami, Swarnali 525  
 Gottlieb, Robert L 122, 395  
 Gottlieb, Sami Lynne 708  
 Gouaux, Ben 327  
 Goverayi, Tendayi 567  
 Govere, Sabina 563, 564, 661, 769  
 Govindaraj, Sakthivel 583  
 Goyal, Parag 393  
 Gozzo, Paolo 472  
 Grab, Joshua 467  
 Grabowski, M Kate 681, 690, 763  
 Grace, Daniel 776  
 Gracias, Ségolène 404  
 Graff, Claus 502  
 Graham, Barney S 608, 618  
 Graham, Bobbie 605  
 Graham, Carl 120  
 Grammatico-Guillon, Leslie 698  
 Grañana-Castillo, Sandra 365, 374  
 Granche, Janeway 667  
 Grant, Alison D 524  
 Grant, Igor 326  
 Grant, Robert 762  
 Grant, Shannon 257  
 Grant-McAuley, Wendy 275, 678, 682  
 Gras, Guillaume 698  
 Grasa, Carlos 620  
 Grassi, Germana 336  
 Grau-Exposito, Judith 207, 278, 300, 306, 386  
 Gravett, Ronnie M 409  
 Gray, Ronald 659, 720, 725  
 Gray-Gaillard, Sophie L 119  
 Grayson, Nicholas 158  
 Grebe, Eduard 640  
 Greco, Chad 294  
 Green, Sandra 258  
 Green, Timothy 704  
 Greene, Rusty 630  
 Greene, Warner 310  
 Greiner, Jared J 493, 500  
 Greninger, Alex 138, 553  
 Grennan, Troy 709  
 Griffith, Bradley 509  
 Grilli, Elisabetta 334  
 Grillo, Michael 173  
 Grimwood, Ashraf 182, 766  
 Grinspoon, Steven 494, 496, 498, 506  
 Grinsztejn, Beatriz 150, 153, 510, 580, 771  
 Grint, Daniel 131  
 Gripshover, Barbara 409  
 Grisetti, Susanna 336  
 Grobler, Jay A 87, 129  
 Groebner, Jennifer L 304, 424  
 Gross, Jessica M 173  
 Gross, Robert 677, 723  
 Gross, Ruediger 213  
 Grov, Christian 637  
 Gruber, Joshua 503  
 Gruenewald, Analise L 347  
 Grundhoff, Adam 482  
 Grunfeld, Carl 98  
 Grunwald, Stephen 439  
 Gu, Wenyi 455  
 Guanira, Juan V 772  
 Guasco, Rick 418  
 Guastamacchia, Giulia 335  
 Gubser, Celine 280  
 Gudipati, Smitha 629  
 Guenther, Patricia 146  
 Guha, Debjani 320  
 Guillén, Sara 597  
 Williams, Martin 215  
 Guiteau, Colette 185  
 Guliani, Sidhant 709  
 Gulick, Roy M 357  
 Gumber, Sanjeev 118  
 Gumbo, Justice Farai 567  
 Gumrukcu, Serhat 381  
 Gunasena, Manuja 214  
 Gunda, Resign 524  
 Gundacker, Holly 147  
 Günthard, Huldrych F 395, 425, 449, 450, 452, 457  
 Guo, Jeffrey Z 187  
 Guo, Kejun 218  
 Guo, Amit 709  
 Gupta, Amita 140, 178, 559  
 Gupta, Kusum 387  
 Gupta, Ravindra 399  
 Gupta, Samir 415, 509  
 Gupta, Sundeep 181  
 Gupte, Nikhil 559  
 Gurrion, Samuel 560  
 Gustafson, Deborah 538  
 Gustafson, Reka 709  
 Gutiérrez Chamorro, Lucía 206  
 Gutierrez, Angela 641  
 Gutierrez, Mar 412  
 Gutierrez, Ximena 772  
 Gutner, Cassidy 110
- H-**  
 Haag, Katharina 727  
 Haagmans, Bart 124  
 Haas, Andreas D 662

- Haddad, Lisa 573, 575  
 Hagins, Debbie 415  
 Haimbe, Prudence 768  
 Haine, Lillian M F 492  
 Hakim, James 94  
 Hall, Eric 636, 638  
 Hall, Irene 108, 655, 731  
 Hallmark, Camden J 653  
 HameiriBowen, Dan 262  
 Hammond, Janet 364  
 Hammonds, Jason E 351  
 Hamzah, Lisa 142, 508, 540  
 Han, Kelong 373  
 Han, Win Min 370  
 Hanekom, Willem A 263, 524  
 Haney, Reed 420  
 Hanke, Jen 257  
 Hanks, Nancy 238, 333  
 Hanley, Timothy 290  
 Hanna, David B 104, 247, 654, 765  
 Hannay, Emma 691  
 Hannon, Kayla 164  
 Hanrahan, Colleen 770  
 Hans, Lucia 689  
 Hans, Verkerke 583  
 Hanscom, Brett 153  
 Hansen, Derek 717  
 Hansen, Olivia I 236  
 Hardy, Isabelle 651  
 Hare, C Bradley 97  
 Harold, Rachel 724  
 Harrell, Tanya 147  
 Harrington, Conn M 541  
 Harris, Barry-Lewis 685  
 Harris, Lynnette L 593  
 Harris, Tiffany G 186, 634  
 Hart, Trevor 776  
 Hartana, Ciputra Adjaya 225  
 Hartig, Heather 254  
 Hartman, Christine M 471  
 Hartnett, Kathleen P 739  
 Harvey-Vera, Alicia 652  
 Hasen, Nina 756  
 Hassan, Shukri 743  
 Hassibi, Arjang A 436  
 Haubrich, Richard H 393, 397, 711, 713  
 Haughey, Norman D 337  
 Häuptle, Micha A 385  
 Hausler, Harry 134  
 Havlir, Diane V 151, 568, 730  
 Hawk, Kathryn 683  
 Hawken, Mark 186  
 Hawkes, Michael T 592  
 Hayes, D Neil 188  
 Hayes, Richard 678, 680, 682, 708  
 Haynes, Barton 268  
 Hayward, Brooke 298  
 Hazuda, Daria 129, 316  
 He, Feng 439, 442, 713  
 Heaney, Christopher D 209  
 Heaps, Amy 428  
 Hears, Anna C 291  
 Heaton, Robert K 101, 325, 326, 328, 348  
 Hecht, Frederick M 254  
 Hecht, Jen 730  
 Heckbert, Susan 98  
 Heckman, Barbara 603  
 Hedt-Gauthier, Bethany 399  
 Hee Lee, Myung 180  
 Heeney, Aoife M 742  
 Heffron, Renee 152  
 Heimbach, Tycho 88  
 Heinrich, Timothy A 627  
 Heinz, Beverly A 426  
 Heirman, Ingeborg 123  
 Heise, Mark 384  
 Heller, Sandra 213  
 Heltsley, Roy 692  
 Hemphill, Linda 495  
 Hendrix, Craig 147  
 Heneine, Walid 146, 297, 714, 715  
 Henny, Kirk Doulgas 701, 703  
 Hensley, Kathryn S 695  
 Hepler, Deborah A 416  
 Herati, Ramin S 119  
 Herbeck, Joshua T 138  
 Herbert, Richard L 271  
 Herbst, Kobus 524, 648  
 Herce, Michael E 600  
 Herman, Gary 123  
 Hermanides, Gonneke 695  
 Herman-Roloff, Amy 635  
 Hermans, Sabine 767  
 Hern, Faye 379  
 Hernandez Gutierrez, Cristina 339  
 Hernández, Concepción 581  
 Hernanz-Lobo, Alicia 616  
 Herold, Betsy 699  
 Herrera, Carolina 361  
 Herrero-Fernández, Inés 235  
 Herrmann, Yannis 633  
 Herth, Felix 633  
 Hewlett, Kendra 372  
 Hiatt, Joseph M 187  
 Hicks, Katherine A 704  
 Hidalgo, Jose 650  
 Higashide, Wendy 388  
 Hightow-Weidman, Lisa 356  
 Hikichi, Yuta 424  
 Hileman, Corriynn O 329, 490, 501  
 Hill, Andrew 517, 572  
 Hill, Collin 384  
 Hill, Shawn 255  
 Hindley, Laura 517  
 Hindman, Jason 375, 415, 430  
 Hines, Jonas 759  
 Hioe, Catarina E 250  
 Hippchen, Theresa 633  
 Hirschfield, Sabina 706  
 Hlongwa, Mbuzeleni 756  
 Ho, Emily 375  
 Ho, Ken 716  
 Ho, Michelle 282  
 Ho, Shu-Yuan 463  
 Ho, Ya-Chi 287, 305  
 Hoang, Timothy 118  
 Hodge, Catherine Elizabeth 378  
 Hodgkins, Paul 397  
 Hoelscher, Michael 557  
 Hoenigl, Martin 529  
 Hoesley, Craig 147, 716  
 Hoffman, Risa M 176  
 Hoffmann, Christian 159  
 Hoffmann, Christopher 770  
 Hoffmann, Udo 494  
 Hofmann, Eveline 449, 450  
 Hofmeyr, Justus 571  
 Hogg, Evelyn 241  
 Høgh, Julie 499, 502  
 Hoh, Rebecca 254, 301  
 Holder, Angela 297, 714, 715  
 Holguin, Anthony 498  
 Hollinger, F Blaine 464  
 Holloway, JaNae 526  
 Holman, Wayne 777  
 Honer, William G 663  
 Hong, Hee-kyung 240  
 Honwana, Nelly 173  
 Honwani, Joseph 675  
 Hootman, Katie 513  
 Hoover, Karen W 106, 696, 701, 703, 731, 739  
 Hoppe, Anne 94  
 Horani, Amjad 188  
 Horberg, Michael A 97, 104, 136, 330, 456, 533, 626, 671  
 Horga, Arantxa 364  
 Horn, Sacha 557  
 Horne, Elizabeth 318, 345  
 Horne, Sarah 684  
 Horner, Anna Marie 621  
 Horowitz, Adam Z 219  
 Horvath, Keith Joseph 603, 706  
 Hosek, Sybil 366, 367  
 Hosseinipour, Mina C 559, 580  
 Hou, Craig E 330  
 Hou, Qingjiang 504, 752  
 Houldsworth, Jane 166  
 Houser, Katherine V 608  
 Houston, Patricia E 230  
 Howard, Rex A 297  
 Howell, Bonnie 316  
 Howell, Pauline JB 562  
 Hoxie, James 84, 199  
 Hrapcak, Susan 173  
 Hrusa, Gili 634  
 Hsiao, Marvin 93, 398, 647  
 Hsieh, Emily 292  
 Hsieh, Hsing-Chuan 318  
 Hsieh, Szu-Min 463  
 Hsieh, Yu-Hsieh 690  
 Hsu, Denise C 154, 359, 407, 408  
 Hsu, Ling 730, 762  
 Hsue, Priscilla 99  
 Hu, Chen 209  
 Hu, Eric 294  
 Hu, Jianfei 82, 193  
 Hu, Nai-Chung 93  
 Hu, Tony 558  
 Hu, Wei-Shau 79, 190  
 Hu, Xiaohong 655  
 Hu, Xiaojun 195  
 Huaman, Moises A 497  
 Huang, Chin-Shiou 162  
 Huang, David 183  
 Huang, Hailin 415, 430  
 Huang, Qian 316  
 Huang, Sung-Hsi 465  
 Huang, Ya-Lin A 696, 703, 731, 739  
 Huang, Yu-Shan 463  
 Huber, Amy 768  
 Hudelson, Sarah Elizabeth 275  
 Hudgens, Michael 603  
 Hudson, Krischan J 401, 402, 541  
 Huff, Bob 418  
 Hughes, Michael 178, 396, 555  
 Huhn, Gregory 110, 122  
 Hui, Qin 232  
 Huik, Kristi 222  
 Huisting, Joanne 629  
 Hulgan, Todd 325, 459, 521, 522  
 Hull, Mark 136, 448, 456, 468, 709  
 Hulter, Henry N 617  
 Humes, Elizabeth 102, 104, 654, 670  
 Humphrey, John Moore 109, 743  
 Humphrey, Sarah 144  
 Hundsberger, Thomas 343  
 Hung, Chien-Ching 132, 463, 465  
 Hung, Rachel K Y 508  
 Hunt, Peter W 98, 254  
 Hunter, Alan 550  
 Hunter, James 313  
 Hunter, Patricia 491  
 Huo, Yanling 593  
 Huprikar, Shirish 467  
 Hural, John 257  
 Hurdiss, Daniel L 385  
 Hurlston Cox, Mackenzie 689  
 Hurst, Jillian H 625  
 Hurt, Christopher B 123  
 Hurt, William 645  
 Huser, Vojtech 475  
 Hussaini, Laila S 621  
 Husson, Jennifer 467  
 Huynh, Christina 248  
 Hwa, Shi-Hsia 263  
 Hwang, Carey 416  
 Hyland, Robert H 127  
 Hyle, Emily P 670  
 Hyman, Sara W 119  
 -I-  
 Iapadre, Nerio 137  
 Ibanescu, Ruxandra-Ilina 651  
 Ibáñez de Garayo, Maité 169  
 Ibegbu, Chris 583  
 Ignacio, Caroline 692  
 Imamichi, Tomozumi 195  
 Imaz, Arkaitz 256, 362, 405, 641  
 Imran, Darma 565  
 Indolfi, Giuseppe 444  
 Inghels, Maxime 753  
 Ingiliz, Patrick 439, 442  
 Innocenti, Giuseppe Pietro 208, 470  
 Inzitari, Rosanna 258  
 Iovi, Cezar 298  
 Ippolito, Giuseppe 545  
 Iqbal, Kashif 106, 701  
 Irby, Les'Shon 583  
 Iribarren, José A 441  
 Iroezindu, Michael 519, 732  
 Irrinki, Alivelu M 294  
 Irwin, David J 347  
 Isa, Flonza 123  
 Isaeva, Natalia 481  
 Ishida, Takaomi 162  
 Isidori, Andrea 208  
 Islam, Jessica Y 103, 141  
 Isnard, Stéphane 298  
 Itell, Hannah L 261  
 Itoh, Megumi 759  
 Ivachtchenko, Alexandre 390  
 Ivanov, Andrey I 198  
 Ivanova Reipold, Elena 446  
 Ivashchenko, Andrey 390  
 Iwamoto, Marian 88  
 Iwasaki, Akiko 165  
 Iyer, Shilpa S 600  
 Iylerdo-Useros, Nuria 259  
 -J-  
 Jackson, Akil 389  
 Jackson, Laurelle 263  
 Jacobs, Jana L 116  
 Jacobson, Cindy 147, 716  
 Jacobson, Denise 573, 575, 576, 611, 613  
 Jacobson, Evin 704  
 Jacobson, Jeffrey 156  
 Jadcak, Stephen 689  
 Jaeger, Hans 401  
 Jaffe, Elaine S 480  
 Jahn, Andreas 585  
 Jain, Mamta K 492  
 Jain, Sonia 439, 442, 713  
 Jakait, Beatrice 743  
 Jamal, Leda F 556  
 Jambo, Kondwani 491  
 Jamil, Muhammad 446  
 Jamison, Kelly 699  
 Jang, Grace 332  
 Jang, Gwendolyn M 187  
 Jang, Jeong Hoon 591  
 Jang, Sunyoung 315  
 Janini, Luiz Mario R 313  
 Jantarabenjakul, Watsamon 601  
 Janus, Scott E 501  
 Jao, Jennifer 573, 575, 590, 613  
 Jarrin, Inmaculada 441, 544, 549  
 Jarvis, Joseph N 645  
 Jasuja, Ria 188  
 Jaszi, Edward G 186  
 Javan, Arzhang Cyrus 396, 555  
 Javier-Espinal, Xiomara 630  
 Jaworowski, Anthony 291  
 Jayanthi, Praveena 739  
 Jean-Juste, Marc-Antoine 185  
 Jean-Philippe, Patrick 176, 177, 609  
 Jefferson, Celeena R 626  
 Jefferys, Laura 615  
 Jeffrey, Jerry L 126, 421  
 Jelcic, Ilijas 343  
 Jenike, Katherine M 315  
 Jenkins, Cathy A 510  
 Jenkins, Heidi 740  
 Jennings, Lauren 398  
 Jeppson, Jeffrey 91, 368  
 Jha, Divya 115, 211, 219  
 Jiang, Chenyang 155, 309  
 Jiang, Ruoyi 165  
 Jiang, Wei 349  
 Jiang, Wenwen 566, 577, 674  
 Jiemenez-Leon, Reyes 194, 224  
 Jilich, David 443  
 Jiménez de Ory, Santiago 597  
 Jiménez, Ana Belén 619  
 Jiménez, Daniel 527  
 Jimenez, Guadalupe 728  
 Jimenez-Gonzalez, Maria 535  
 Jiménez-Moyano, Esther 264, 265, 281  
 Jin, Chan 656  
 Jin, Sunghee 515  
 Jo, Youngji 768  
 Joanita, Kigozi 729

- Joao, Esau 506  
 Jochmans, Dirk 387  
 Jogiraju, Vamshi 375  
 Johnson, Bethany 367  
 Johnson, Brent A 95  
 Johnson, Chad J 291  
 Johnson, Cheryl C 446, 674  
 Johnson, Dylan M 426  
 Johnson, John 130  
 Johnson, Katherine 576  
 Johnson, Kelly Anne 354, 355  
 Johnson, Kirsten A 436  
 Johnson, Leah 728  
 Johnson, Leigh 614  
 Johnson, Margarate A 414, 540, 550  
 Johnson, Pafio 728  
 Johnson, Sherri 716  
 John-Stewart, Grace 558, 560, 566, 577, 674, 707, 710  
 Johnston, Benjamin 177  
 Johnston, Carrie 513  
 Johnston, Rowena 156, 289  
 Jollimore, Jody 776  
 Jones Weiss, Deborah 260, 538, 539  
 Jones, Bradley R 283  
 Jones, Bryan E 426  
 Jones, Dean P 512  
 Jones, Mathew 158  
 Jones, Norman 220, 254  
 Jones, R Brad 305  
 Jones, Rachael 540  
 Jordan, Michael R 433  
 Jordans, Carljin 124, 391, 392, 695  
 Joseph Davey, Dvora L 149  
 Joseph, Patrice 185  
 Joseph, Philip 755  
 Joseph, Rachael 635  
 Joseph, Sarah B 341, 344  
 Joshi, Samit R 126  
 Joska, John 398, 662  
 Joy, Jeffrey B 283  
 Joyce, M Gordon 268  
 Juchnowski, Steven M 497  
 Juegl, Boris 274  
 Jugé, Lauriane 162  
 Julius, Hilton 750  
 Jung, Ikrak 515  
 Junghae, Muthoni 435  
 Junker, Christoph 139  
 Juraska, Michal 718  
 Justice, Amy 99, 102, 232, 454, 521, 523, 671  
 Justman, Jessica 649
- K-**  
 Kabaghe, Alinune 634  
 Kabami, Jane 151  
 Kabanda, Siti 93  
 Kabatesi, Donna 729  
 Kabogozo, Julian 368  
 Kacane, Deborah 573, 575  
 Kachimbe, Memory 477  
 Kaech, Susan 244  
 Kaelber, David 520  
 Kagaayi, Joseph 659, 681, 690, 720, 725, 763  
 Kagimu, Enock 131  
 Kagoli, Mathew 634  
 Kahl, Lesley P 489  
 Kaimal, Arvind 94  
 Kaiser, Kristen Nicole 271  
 Kalan, Anil 675  
 Kaleebu, Pontiano 158, 690  
 Kalema, Nelson 729  
 Kallewaard, Nicole 426  
 Kallianpur, Asha R 325  
 Kallianpur, Kalpana 333  
 Kalou, Mireille B 675  
 Kalua, Thoko C 746  
 Kalua, Thokozani 585  
 Kambu, Andrew D 94, 758  
 Kamen, Amine 267  
 Kamis, Kevin F 546  
 Kammers, Kai 275  
 Kamng'ona, Raphael 491  
 Kampamba, Davies 759  
 Kamy, Moses R 151  
 Kanaprach, Ratchapong 179  
 Kandala, Bhargava 376  
 Kang, Chil-Yong 267  
 Kanjanavanit, Suparat 595  
 Kankaka, Edward N 720, 763  
 Kantor, Amy 496  
 Kanyenda, Rachel 746  
 Kaplan, Jacob 203  
 Kaplan, Robert 247  
 Kapoor, Andrew 588  
 Kapoor, Manav K 302  
 Karakousis, Petros 559  
 Karg, Carissa 257  
 Karim, Farina 263  
 Kariminia, Azar 614  
 Karlic, Rosa 166  
 Karmacharya, Trishala 119  
 Karn, Jonathan 248, 288, 289  
 Karris, Maile 110, 671  
 Karuna, Shelly 257, 718  
 Karwacz, Katarzyna 233  
 Kasaie, Parastu 102, 668, 670, 775  
 Kasaro, Margaret P 578, 579  
 Kashanchi, Fatah 197, 249  
 Kashuba, Angela 203, 356, 357, 360, 362, 363  
 Kasibante, John 131  
 Kasonde, Prisca 186  
 Kasozi, Charles 614  
 Kassanjee, Reshma 614  
 Kassaye, Seble 168, 230, 433, 526, 724  
 Kassiotis, George 120  
 Kasten, Mary J 380  
 Kasturiratna, Dhanuja 214  
 Katbi, Moses 736, 774  
 Katlama, Christine 148, 419, 429, 511, 537  
 Kato, Darryl 717  
 Katsikis, Peter 124  
 Kattan, Meyer 611  
 Katusiime, Mary-Grace 594  
 Katz, David 674  
 Katzenstein, David 433  
 Kaufmann, Daniel Elias 303  
 Kaur, Jasmine 294  
 Kauzlaric, Annamaria 308  
 Kavanagh, Eoin 96  
 Kawata, Kristin 89  
 Kawatachi, Jon 737  
 Kay, Emma 105  
 Kayange, Noel 716  
 Kayigamba, Felix 634  
 Kaytes, Andy 418  
 Kazadi, Mwayabo Jean Claude 477, 679  
 Kazemian, Pooyan 771  
 Ke, Ruian 125  
 Kearney, Mary F 116, 255, 299, 304, 424, 594, 639  
 Kechris, Katerina 218  
 Keele, Brandon 84, 199, 201, 277  
 Kegg, Stephen 508  
 Keitel, Wendy A 464  
 Kelleher, Anthony 314, 551  
 Kelley, Colleen F 547  
 Kelley, Kristen 714  
 Kelly, Christine 231, 491  
 Kelly, Erin 318  
 Kelly, Matthew S 625  
 Kelvin, Elizabeth A 109  
 Kempf, Mirjam-Colette 526, 539  
 Kendall, Claire 484  
 Kenney, Adam D 383  
 Kenny, Grace 258  
 Kerndt, Peter 660  
 Kerr, Stephen J 370  
 Kerrigan, Deanna 602  
 Kersey, Kathryn 617  
 Keruly, Jeanne C 543, 734  
 Kesavan, Vasudevan Canjeevaram 145, 719  
 Keshavarzian, Ali 114  
 Kettelhut, Aaren 214, 530  
 Keys, Jessica 341  
 Kgole, Samuel N 590  
 Khadka, Pragma 305  
 Khaitan, Alka 591  
 Khalil, George 714  
 Khan, Javed 230  
 Khan, Shaikat Khan 181  
 Kharfen, Michael 643  
 Khoo, Saye 175, 358, 361, 365, 378, 491  
 Khosa, Perminder 765  
 Khosropour, Christine 665  
 Khubone, Thokozani 754  
 Khumalo, Anele R 769  
 Kibuuka, Hannah 519, 557, 732  
 Kigozi, Darix Ssebagala 659  
 Kigozi, Godfrey 659, 720, 725, 763  
 Kihara, Masahiro 658  
 Kileel, Emma 498, 506  
 Kilgore, Collin B 319  
 Kilpeläinen, Athina 264, 265  
 Kim, Ahra 565  
 Kim, Arthur Y 459  
 Kim, Evelyn 634, 746  
 Kim, H Nina 136, 456, 468, 543  
 Kim, Hae-Young 753  
 Kim, Insook 202  
 Kim, June-Ho 495  
 Kim, Sangwon F 515  
 Kim, Yuriy 249  
 Kimberlin, David 617  
 Kimhofer, Torben 686  
 Kimura, Izumi 113  
 Kincer, Laura 344  
 Kinder, Clifford A 417  
 Kindra, Gurpreet 173  
 King, Rachel 180  
 Kinghorn, Anthony 134  
 Kinloch, Natalie N 283  
 Kinloch-de Loes, Sabine 262, 550  
 Kinslow, Jennifer 311  
 Kintu, Kenneth 175  
 Kinuthia, John 427, 560, 566, 577, 674, 707, 710  
 Kinvig, Hannah 374, 377, 378, 606  
 Kipke, Michele 221  
 Kiptinness, Catherine 721, 722  
 Kiragga, Agnes 94  
 Kirchoff, Frank 112, 213  
 Kirk, Gregory D 103, 141, 536  
 Kirky, Nikolai 452  
 Kirkegaard, Cristina 207  
 Kirkham, Deborah 684  
 Kiser, Jennifer 92, 366, 367  
 Kitahata, Mari M 136, 409, 410, 411, 468, 543, 654  
 Kitao, Peninah 674  
 Kitchen, Philip J 633  
 Kitsios, Georgios D 116  
 Kityo, Cissy M 94, 497  
 Kizhlo, Svetlana 414  
 Klaes, Christoph 686  
 Kleger, Alexander 213  
 Klein, Eili 140  
 Klein, Marina B 136, 448, 456, 468, 671  
 Klein, Nigel 491  
 Klein, Sabra L 140, 209  
 Klekotka, Paul 121, 122  
 Klenerman, Paul 158  
 Klimkait, Thomas 400, 431  
 Klindera, Kent 736, 774  
 Klock, Ethan 678, 680, 682  
 Klopfer, Stephanie O 416  
 Klug, Elizabeth 382  
 Knapp, Jason J 267  
 Knight, Rob 348  
 Knobel, Hernando 641  
 Knorr, Jack 121  
 Knowles, Zak 484  
 Knudsen, Andreas Dehlbæk 499, 502  
 Knudtson, Kelly 356  
 Køber, Lars 499, 502  
 Kobinger, Gary 267  
 Kochhar, Shivani 637  
 Koen, Frederic 761  
 Koenig, Ellen 415  
 Koenig, Serena 184  
 Koepke, Lennart 213  
 Koepfel, Lisa 633  
 Koethe, John 510, 521, 522, 523, 531  
 Kofoed, Klaus Fuglsang 499, 502  
 Kofron, Ryan 711, 713  
 Kohorn, Lindsay 333  
 Koletar, Susan L 526  
 Koloane, Nthabiseng 747, 749, 750  
 Kolson, Dennis L 347  
 Konda, Kelika Anne 772  
 Kong, Ling 462  
 Kong, Xiang-Peng 250  
 Konno, Yoriyuki 113  
 Koofhthille, Catherine K 286  
 Koole, Olivier 524  
 Koopmans, Marion 124  
 Koostra, Neeltje A 237  
 Kopycinski, Jakub 262  
 Korutaro, Violet 177  
 Kosalaraksa, Pope 595, 601  
 Kosco, Julia 329  
 Koshy, Jane 458  
 Kosloff, Barry 680  
 Košmider, Ewelina 239  
 Kosovitsas, Athanasios 550  
 Koss, Catherine A 151, 568  
 Kossenkov, Andrew 114  
 Krotman, Jay R 136  
 Kottlil, Shyam 467  
 Kouamou, Vinie 433  
 Koup, Richard A 82, 86, 117, 160, 192, 193, 271, 273, 608  
 Kourtis, Athena 106, 152, 731  
 Kovacs, Colin 305  
 Kozacka, Katie A 546  
 Kozlowski, Pamela A 618  
 Krakower, Douglas 685, 773  
 Kramer, Jennifer R 471  
 Kravchenko, Dmitry 390  
 Krishnan, Sonya 559  
 Kroch, Abigail 484  
 Krogan, Nevan J 187  
 Kroidl, Inge 557  
 Kronfli, Nadine 651  
 Kronmann, Karl 483  
 Kroon, Eugene 154, 163, 179, 311, 323, 340, 359, 407, 408, 672  
 Krotje, Chelsea 176  
 Krovci, Archana 728  
 Krown, Susan 169  
 Krows, Meighan 111, 563, 564  
 Krueger, Jana 213  
 Krystal, Mark 421, 422  
 Kuchukhidze, Salome 766  
 Kudirick-Downey, Lauren 427  
 Kufa-Chakezha, Tendesayi 757  
 Kufera, Joshua T 315  
 Kuhl, Jørgen Tobias 499  
 Kuhlen, Klaus 686  
 Kulikova, Maria 372  
 Kulkarni, Sarah G 637  
 Kulzer, Jayne Lewis 635  
 Kumar, Amit 296  
 Kumar, Amrendra 214  
 Kumar, Muniratnam S 447  
 Kumar, Princy N 506, 525, 724  
 Kumari, Namita 197, 230  
 Kumta, Nikhil A 211  
 Kumwenda, Johnstone 559, 580  
 Kundu, Suman 521, 523  
 Kuniholm, Mark H 538  
 Kuo, Ching-Hua 132  
 Kurbatova, Ekaterina 130  
 Kuri-Cervantes, Leticia 277, 282  
 Kuritzkes, Daniel R 609  
 Kurland, Irwin J 590  
 Kuster, Herbert 425  
 Kutluay, Sebla B 188  
 Kutsch, Olaf 247  
 Kvaratskhelia, Mamuka 420  
 Kwon, Douglas S 495  
 Kwon, Young Do 85  
 Kwong, Peter D 85
- L-**  
 Labbato, Danielle 329, 501  
 Labhardt, Niklaus D 400, 431  
 Laboune, Farida 193  
 LaBranche, Celia 268  
 Lachowsky, Nathan 776  
 Lacombe, Karine 419, 443  
 LaCourse, Sylvia 558, 560

- Ladinsky, Mark S 115, 116  
 Laeyendecker, Oliver 275, 341, 447, 678, 680, 681, 682, 690  
 Lafrance, Marc-Alexander 267  
 Lagarde, Maria 339  
 Lage, Silvia 170  
 Laghedem, Camilla 476  
 Lahiri, Cecile D 324, 512, 547  
 Lai, Jun 315  
 Lai, Ming-Tain 129  
 Laia Henriques, Júlio Joel 205  
 Laidlaw, Elizabeth 243  
 Lain, Maria Grazia 245, 246, 286  
 Laird, Gregory 315  
 Laird, Kate 664  
 Lake, Jordan 526, 530  
 Laker-Oketta, Miriam 486  
 Laketa, Vibor 394  
 Lal, Alan 776  
 Lallemand, Marc 444  
 Lam, Jennifer O 97, 330  
 Lama, Javier R 252, 287, 530, 559  
 Lambert, Gilles 776  
 Lambert, John Shearer 100, 231, 742  
 Lambert-Niclot, Sidonie 419, 429  
 Lamonja-Vicente, Noemi 210, 264  
 Lamorde, Mohammed 90, 175, 368  
 Lan, Kristine 553  
 Lana, Erica 308  
 Landay, Alan 96, 100, 114, 156, 247, 248, 288, 311, 523, 528, 529  
 Landes, Megan 585  
 Landete, Pedro 216  
 Landman, Roland 419  
 Landovitz, Raphael J 150, 153, 366, 367, 711, 713  
 Landraud, Luce 582  
 Lane, Cliff 202  
 Langenegger, Eduard J 171  
 Langner, Charlotte 201  
 Lanièce Delaunay, Charlotte 448  
 Lankowski, Alexander 495, 650  
 LaPak, Kyle M 188  
 Laporte, Annalena 302  
 Lapp, Stacey A 621  
 LaPrade, Ellen A 436  
 Larman, Harry B 275  
 Larsen, Anna 474, 577  
 Larue, Ross C 383  
 Laserson, Uri 261  
 Laskow, Thomas 536  
 Lasry, Arielle 143  
 Lataillade, Max 126, 422  
 Lau, Bryan 734  
 Lau, Jillian SY 301  
 Laudari, Carlos G 186  
 Lauffenburger, Douglas A 274  
 Laurent, Emeline 698  
 Laurenzi, Christina 589  
 Laverdure, Sylvain 195  
 Lavoie, Stephanie 592  
 Lavoile, Kerlyne 184  
 Law, G Lynn 84  
 Law, Kenneth 302  
 Lawler, Leo 100  
 Lawrence, David S 645  
 Lawrence, Sarah 142  
 Lawrence, Scott P 199  
 Lawson, Dana Q 188  
 Layman, Laura 288, 692  
 Lazar, Rachael 765  
 Lazarus, Jeffrey V 443  
 Lazzarin, Adriano 415  
 Le Hingrat, Quentin 404  
 Le, Mylinh H 150  
 Leal, Lorna 228  
 Leal, Manuel 235  
 Leбина, Limakatso 133, 134, 361  
 Lebouché, Bertrand 651  
 Lechiile, Kwana 645  
 Lederman, Michael M 227, 529  
 Ledgerwood, Julie E 160, 608  
 Lee, Ashley 314  
 Lee, Brian 211  
 Lee, Catherine 330  
 Lee, Esther 268  
 Lee, Fairlie 177, 572  
 Lee, Guinevere Q 305  
 Lee, Jennifer S 104, 654  
 Lee, John J 164  
 Lee, Kema N 675  
 Lee, Lana 646  
 Lee, Max 299  
 Lee, Ming Jie 142  
 Lee, Monica 629  
 Lee, Sulggi A 191  
 Leeme, Tshepo B 645  
 Legbedze, Justine 590  
 Lemmin, Thomas 85  
 Lennon, Denni 680  
 Leoncikaite, Marija 231  
 Leon-Cruz, Jorge T 178  
 Lepik, Katherine J 432  
 Lerner, Grigoriy 80, 196  
 Leselbaum, Anne R 161  
 Lesko, Catherine 734  
 Lesosky, Maia 93, 149, 568, 647  
 Lessells, Richard 263  
 Letang, Emili 405  
 Letendre, Scott 101, 325, 326, 327, 328, 331, 518  
 LeTourneau, Noelle 762  
 Letsie, Mosilinyane 761  
 Leu, Cheng-Shiun 398  
 Levert, Angélique 362  
 Levine, Andrew 324, 338  
 Levine-Hall, Tory 97  
 Levit, Rebecca 118  
 Levitan, Emily 105  
 Levitt, Daniel 733  
 Levy, Lisa 427  
 Levy, Melissa 756  
 Lewin, Sharon 280, 301  
 Lewis, Lara 754  
 Leyden, Wendy 330, 626  
 Leyre, Louise 219  
 Leysens, Carlien 88  
 Li, Chenglei 79  
 Li, Fan 221  
 Li, Hongxia 294  
 Li, Jianmin 108  
 Li, Jianrong 383  
 Li, Jonathan 156, 276, 311, 312, 437, 555  
 Li, Jun 104, 504, 654, 752  
 Li, Linying 728  
 Li, Mengchun 562  
 Li, Pui-Kai 383  
 Li, Sue 257  
 Li, We 591  
 Li, Wei 293  
 Li, Xiaolin 490  
 Li, Yijia 437  
 Li, Yue J 267  
 Lian, Xiaodong 155, 309, 598  
 Liang, Richard 283  
 Liang, Shuting 397  
 Lichterfeld, Mathias 155, 224, 225, 286, 307, 309, 598, 609  
 Lichtner, Miriam 137  
 Lickert, Heiko 213  
 Lifson, Jeffrey D 82  
 Lifson, Jeffrey 408  
 Lim, Joseph K 136  
 Lima, Viviane D 102, 663, 664, 671, 709  
 Lin, Bob C 160  
 Lin, Nina 514  
 Lin, Shu-Wen 132  
 Lin, Xionghao 198  
 Lin, Ya-Ting 132  
 Lin, Zeyu 421  
 Linardos, Giulia 172  
 Linas, Benjamin 135  
 Lindesmith, Lisa C 618  
 Lindsay, Joanne 484  
 Lindsey, Jane C 603  
 Ling, John 89, 369, 375  
 Linley, Laurie 687, 688  
 Liroff, Kaitlin 724  
 Lisco, Andrea 243  
 Little, Callum 550  
 Little, Kristen 756  
 Little, Susan J 434, 705  
 Littlefield, Kirsten 209  
 Liu, Albert 147, 716, 735  
 Liu, Chung 379  
 Liu, Hui 438  
 Liu, Jocelyn 323  
 Liu, Po-Ting 285  
 Liu, Qin 114, 156  
 Liu, Qingbo 236, 271  
 Liu, Wen-Chun 132, 463, 465  
 Liu, Yang 88  
 Liu, Ya-Pei 127  
 Liu, Yuxin 166, 473  
 Liu, Zhixin 162  
 Livanos, Alexandra E 115, 211, 219  
 Livia, Piccioni 622  
 Liyanage, Namal 214  
 Llamoso, Cyril 422  
 Llano, Anuska 161  
 Llibre, Josep Maria 405, 413, 489  
 Lloyd, Andrew 377, 378  
 Lo Caputo, Sergio 748  
 Lo Re, Vincent 136, 454, 456, 468  
 Lo, Janet 506  
 Lobo, Judith Diane 327  
 Loch, Ana P 556  
 Lockman, Shahin 176, 177, 571, 576  
 Lodha, Manivel 233  
 Lofgren, Sarah 321  
 Logan, Joseph E 656  
 Logue, Jennifer K 261  
 Lomakin, Nikita 390  
 Long, Bradley 202  
 Longenecker, Chris T 495, 497  
 Loo, Theoren 110  
 Looby, Sara E 496  
 Looker, Katharine J 708  
 Loose, Rebecca 557  
 Lopes, John 182  
 López Cortés, Luis Fernando 489, 527  
 Lopez, Juan 544, 581  
 López, Juan C 549  
 Lopez, Miriam Bailon 161  
 López-Galindez, Cecilio 226  
 López-Huertas, María Rosa 159, 527  
 Lopez-Varela, Elisa 660  
 Lopman, Ben 636, 638  
 Lorang, Cynthia G 625  
 Lorens, James 389  
 Lorenz, David 320  
 Lorenzini, Patrizia 242, 334, 545  
 Louie, Alexander 569  
 Louveaux, Marion 78  
 Lovasi, Gina S 649  
 Lozano, Francisco 412  
 Lu, Austin 621  
 Lu, Bing 717  
 Lu, Chuanyi M 191  
 Lu, Michael T 494  
 Lucas, Gregory M 447, 719, 737  
 Lucic, Bojana 394  
 Luckett, Patrick H 164  
 Luckett, Rebecca 571  
 Luisi, Nicole 636, 638  
 Luk, Hugh 238  
 Luke, Brian 222  
 Lumano-Mulenga, Priscilla 768  
 Lumbala, Petronella 477  
 Lumpa, Mwansa 600  
 Lund, Crick 662  
 Lundgren, Jens D 443  
 Luo, Feijun 656  
 Luo, Zhenwu 349  
 Lurain, Kathryn 167, 170, 475, 480  
 Lusi, Osborn 566, 577  
 Lusic, Marina 394  
 Lusso, Paolo 86, 236, 271  
 Lustig, Gila 263  
 Lutalo, Tom 659, 690, 720, 725, 763  
 Lutz, Justin 89  
 Lutz, Thomas 439, 442  
 Luz, Paula M 771  
 Lyamuya, Rita 509  
 Lynch, Kara A 627  
 Lyon, Christopher 558  
 Lyons, Michael S 683  
 -M-  
 Ma, Jimmy 409  
 Maartens, Gary 371, 662  
 Mabhena-Ngorima, Nicoletta 182, 766  
 Mabula-Bwalya, Chileshe 578  
 Mabuta, Judith 571, 576, 588  
 Mabuto, Tonderai 770  
 Macatangay, Bernard 241, 311  
 MacGregor, Louis 440  
 Machekano, Rhoderick 746  
 Macias, Juan 445, 466, 469  
 Macius, Youry 185  
 Macken, Alan 96  
 MacLaren Ehui, Lynsay 110, 311  
 MacMillan, Daniel 283  
 MaCoy, Lisa S 621  
 MacPherson, Peter 133  
 MacRae, James I 120  
 Madeen, Erin 255  
 Madhira, Vithal 103, 141  
 Madlala, Hlengiwe 574  
 Madrugá, Jose VR 556  
 Magedson, Ariana 261  
 Maggiolo, Franco 748  
 Magombedze, Gesham 312  
 Mahajan, Supriya Dinkar 346  
 Maheu-Giroux, Mathieu 448, 733  
 Mahieux, Renaud 249  
 Mahmood, Maryam 380  
 Mahnken, Jonathan 504  
 Mahon, Niall 100  
 Mahoney, Kevin B 642  
 Mahony, Mary 298  
 Mahwire, Tamirirash Christopher 747  
 Mahy, Mary 646  
 Maida, Alice N 746  
 Maile, Khotso 182  
 Mailliard, Robbie B 200  
 Maina, Mercy 109, 743  
 Major, M Ben 188  
 Mak, Lily 369  
 Makaba, Ziyanda 747  
 Makarova, Natalia 715  
 Makhema, Joseph 571, 576, 588, 590, 609  
 Makhosazana, Makhanya 675  
 Maki, Pauline 322  
 Makinson, Alain 537  
 Makumbi, Fred 725, 763  
 Makuwaza, Lynette 689  
 Malaba, Thokozile R 93, 175  
 Maldarelli, Frank 222, 255, 304, 408  
 Maleche-Obimbo, Elizabeth 558, 611  
 Malee, Kathleen 593  
 Maleesatharn, Alan 601  
 Malele, Faustin 186  
 Maleno, Maria Jose 228  
 Malhotra, Meena 366, 367  
 Malik, Mannat 657  
 Maliqi, Liridona 85  
 Mallal, Simon 523  
 Mallewa, Jane 491  
 Mallipeddi, Vishnu Priya 533  
 Mallon, Patrick 96, 100, 231, 258, 491  
 Malmström, Stina 487  
 Malone, Shawn T 756  
 Malone, Todd 747, 749, 750  
 Malunda, Bernadette Vimbayi 567  
 Malvestutto, Carlos 496, 506  
 Man, Choy 414  
 Manabe, Yukari C 209  
 Mañalich-Barrachina, Laura 278  
 Manda, Samuel 757  
 Mandelbrot, Laurent 570, 582  
 Maness, Nicholas 84, 199  
 Manganare, Marcos 146  
 Mangusan, Ralph 167, 480  
 Manickam, Arun A 436  
 Manion, Maura 170, 243  
 Manly, Jennifer J 332  
 Manmathan, Gavin 550  
 Mann, Jamie J 267  
 Manno, Emma 172

- Mannon, Roslyn B 103  
 Manresa-Dominguez, Josep Maria 210  
 Mansergh, Gordon 706  
 Mantero, Alejandro 260  
 Manuzak, Jennifer A 667  
 Manyike, Peter 675  
 Manzanarez, Angela 616  
 Manzardo, Christian 412  
 Mao, Jianbin 525  
 Mao, Linyong 215  
 Maphosa, Thulani 746  
 Maponga, Charles C 567  
 Maqwadini, Zandile 574  
 Mar, Hanna 241  
 Mara, Elise S 730, 762  
 Marathe, Gayatri 448  
 Marcelin, Adias 185  
 Marcelin, Anne Genevieve 429, 511  
 Marchand, Arnaud 387  
 Marchand, Lucie 570  
 Marchant, Rebecca 142  
 Marchi, Emanuele 158  
 Marconi, Vincent 95, 232, 399, 510, 521, 547, 654  
 Marcus, Julia 773  
 Marfil, Silvia 226, 259  
 Margevicius, Seunghee 497  
 Margolis, David M 204, 401  
 Margolis, Leonid 227  
 Margot, Nicolas 127, 128  
 Maricato, Juliana T 313  
 Marignani, Massimo 137  
 Marin, Miguel 210, 281  
 Marinaro, Letizia 335  
 Mariño, Ana 227  
 Markowitz, Martin 253  
 Markowitz, Norman 629  
 Maroko, Andrew 637  
 Marovich, Mary 121  
 Marques de Menezes, Erika 310  
 Marques, Ernesto T A 116  
 Márquez, Elena 581, 616  
 Márquez-Arce, Daniel 226  
 Marra, Christina M 101  
 Marsh, Mark 84, 199  
 Marshall, Deborah 478  
 Marshall, Vickie Ann 480  
 Martel-Laferrrière, Valérie 448  
 Martí, Anna 194  
 Martin Carbonero, Luz 453  
 Martin, Charlene 404  
 Martin, Eileen 338  
 Martin, Hal 369, 415, 430  
 Martin, Holly A 191  
 Martin, Jeffrey N 254, 486  
 Martin, Malcolm A 82, 86  
 Martin, Natasha 439, 440, 442  
 Martin, Ross 425, 430  
 Martin, Shayanne 163  
 Martin, Thomas 520  
 Martín-Carbonero, Luz 460  
 Martínez, Esteban 393, 641  
 Martínez-Caceres, Eva 210, 264, 265  
 Martínez-Delgado, Gustavo 115, 211, 219  
 Martínez-Picado, Javier 300  
 Martínez-Román, Paula 159  
 Martínez-Sanz, Javier 527  
 Martín-Gayo, Enrique 216, 225, 269  
 Martins, Mauricio A 270  
 Martinson, Neil A 133, 134, 361  
 Martín-Vicente, María 549  
 Martyn, Emily 131  
 Maruri, Fernanda 565  
 Marwa, Mary 707, 710  
 Marzinke, Mark 147, 153  
 Masasa, Gosego N 590  
 Mascola, John R 82, 86, 160, 273, 608  
 Masenya, Masebole 572  
 Masette, Godfrey 399  
 Mashayekhi, Mona 531  
 Mashele, Nyiko 149  
 Masheto, Gaerolwe 177, 178  
 Masiá, Mar 413  
 Masip, Jenifer 194  
 Maskew, Mhairi 764  
 Massaccesi, Guido 217, 289, 461  
 Massad, L Stewart 168  
 Massana, Nuria 207, 278, 386  
 Massanella, Marta 206, 259, 265, 595  
 Massud, Ivana 714  
 Masters, Jeff 551  
 Masters, Mary Clare C 518  
 Mastroianni, Claudio Maria 208, 470  
 Mastrorosa, Ilaria 334  
 Masur, Henry 467  
 Maswabi, Kenneth 609  
 Maswai, Jonah 557, 732  
 Masyuko, Sarah 427  
 Matemo, Daniel 560, 566, 577, 674  
 Mateu, Lourdes 259, 265  
 Mathema, Barun 649  
 Mathenjwa, Thulile 753  
 Mathiba, Ruth 605  
 Mathon, Jean Edouard 185  
 Matías-Florentino, Margarita 251  
 Matibe, Petronella 567  
 Matos, Miriam 333  
 Matsen IV, Frederick 261  
 Mattem, Jeremie 582  
 Matthews, Gail 551, 552  
 Matthews, Jessica 489  
 Matthews, Philippa 753  
 Matthews, Randolph P 87, 88, 376  
 Matulionyte, Raimonda 443  
 Matus Nicodemus, Rodrigo 192  
 Maury, Wendy 389  
 Mauss, Stefan 439, 442  
 Mave, Vidy 559  
 Maves, Ryan C 318, 483  
 MaWhinney, Samantha 92, 354, 355, 546  
 Mawlana, Sajeeda 91  
 Maxwell, Heather 617  
 Maxwell, Nicky 662  
 Mayaud, Philippe 708  
 Mayer, Craig 475  
 Mayer, Cynthia 752  
 Mayer, Kenneth H 409, 410, 411, 530, 543, 735  
 Mayer, Magdalene 173  
 Mayhew, Christopher 351  
 Maynes, Mark 189  
 Mayondi, Gloria 571, 576, 588  
 Mayor, Angel 136, 468, 671  
 Mayoral-Muñoz, Mario 534  
 Mayrhofer, Thomas 494  
 Mazonson, Peter 110  
 Mazroue, Sepideh 251, 653  
 Mazzotta, Valentina 336, 545  
 Mbabazi, Leah 368  
 Mburu, Margaret 635  
 MC Gomes, André 205  
 McAlpine, Lindsay 165  
 McArthur, Justin 337  
 McCallum, Sara 498  
 Mccan, Kaitlyn 517  
 McCann, Kathleen 258  
 McCarthy, Geraldine 96  
 McCarthy, Katie 177, 587, 604  
 McCarthy, Kimberly D 435  
 McCauley, Marybeth 150, 153, 580  
 McClure, Tara 147  
 McCluskey, Suzanne 95, 399  
 McCollum, Jeffrey 108, 655  
 McComsey, Grace A 329, 490, 497, 501, 503, 548, 613  
 McConkey, Sam 96  
 McCoy, Laura E 120, 262  
 McCrary, Andrew 612  
 McCurdy, Lewis 406  
 McCutchan, J Allen 101  
 McDermott, Adrian 86, 117, 160, 609  
 McEvoy, Robin 593  
 McFadden, Ryan 294  
 McFall, Allison M 145, 447, 719, 737  
 McFarland, Elizabeth J 608  
 McGettrick, Pdraig 100, 231, 258  
 McGinnis, Kathleen A 626, 671  
 McGinty, Tara 96, 742  
 McGowan, Catherine 510, 565  
 McGowan, Ian 161  
 McGrath, Nuala 753  
 McHenry, Megan 591  
 McLleron, Helen 371  
 McKellar, Mehri 673  
 McKhann, Ashley 528, 529  
 McLinden, Taylor 664  
 McMahan, Cynthia 318, 345  
 McMahon, Deborah 222, 241, 304  
 McMahon, Devon 486  
 McMahon, James 280, 301  
 McNairy, Meredith 630  
 McNeese, Marlene 653  
 McNicholl, Ian 406  
 McNicholl, Janet 146  
 McNiff, Kimberly 525  
 McPhail, Mark 395  
 Mecha, Jerphason Ongayo 560  
 Medina, Juan C 350  
 Medina, Karla 234, 310  
 Medley, Amy 143, 173  
 Meeds, Heidi 462  
 Meeker, Karin L 164  
 Mehandru, Saurabh 115, 211, 219  
 Mehta, Christina 706  
 Mehta, Cyra C 512, 526  
 Mehta, Sanjay R 326, 632, 652  
 Mehta, Shruti H 145, 447, 536, 694, 719, 737  
 Mejia, Fernando 510  
 Melaku, Zenebe 186  
 Melbourne, Kathleen 494  
 Mellins, Claude A 593  
 Mellors, John W 116, 241, 304, 311, 424, 427, 428, 594  
 Melo, Marineide Gonçalves 580  
 Melvin, Ann J 604  
 Mena-Garay, Beatriz 534, 535  
 Mendes Fernandes, Susana 205  
 Mendez-Echevarria, Ana 617  
 Mengistu, Yohannes 761  
 Mensah, Gifty 249  
 Mensah, Gloria 83  
 Menza, Timothy William 144  
 Menzies, Dick 561  
 Meri, Helina 736, 774  
 Merino, Dolores 469  
 Merkulova, Elena 390  
 Merle, Uta 633  
 Mermin, Jonathan 704  
 Metcalf, Nicholas 317  
 Meya, David 131  
 Meyer, Laurence 537  
 Meyer, Megan F 661  
 Meyers, Caren 379  
 Meyers, Kathrine 630  
 Mfuno, Towela Nyapangula 679  
 Mgbako, Ofole 398  
 Mgodini, Nyaradzo M 718  
 Mhlanga, Laurette 640  
 Mhlongo, Dumisani 675  
 Miao, Hongyu 530  
 Miao, Huiyi 236, 271  
 Mican, Rafael 339, 413, 534, 544, 549  
 Miceli, Janet 740  
 Michel, Katherine G 168, 247  
 Micheni, Murugi 721  
 Michos, Erin D 324, 538  
 Mickens, Kaylee 218  
 Mickleam, David R 389  
 Midkiff, Cecily 347  
 Mighetto, Lorenzo 335  
 Mihaljevic, André 633  
 Milam, Joel 168, 539  
 Miller, Kristen 284  
 Miller, Lori 708  
 Miller, Rachel L 283  
 Mills, Anthony 220  
 Mills, Lisa 659, 720  
 Mills, Patrick 297  
 Milton, Thandi 645  
 Milush, Jeffrey 254, 301  
 Minassian, Caroline 454  
 Minchella, Peter 679, 759  
 Mine, Madisa 645  
 Minkoff, Howard 168  
 Miot, Jacqui 764  
 Miremba, Grace 94  
 Miro, Jose M 159, 405, 412  
 Mirochnick, Mark 605, 606, 607  
 Mirza, Ayesha 613  
 Mirzayi, Chloe 637  
 Misamore, Johnathan 86  
 Mishra, Sharmistha 733  
 Misner, Dinah 387  
 Misra, Anisha 295  
 Misra, Vikas 320  
 Mitchell, Brooks 238  
 Mitchell, Hannah 645  
 Mitchell, James 146, 297, 715  
 Mitchell, Julie 154, 595  
 Mitchell, Kate M 669, 733, 735  
 Mitha, Essack 126  
 Mittl, Peer 85  
 Mmalane, Mompoti 576, 588  
 Mmasa, Keolebogile N 590  
 Mngadi, Kathy 718  
 Mngqibisa, Rosie 91, 401, 559  
 Moanna, Abeer 547  
 Mohammedi, Bharat 122  
 Mcroft, Amanda 443, 452, 532  
 Modolo, Eliana 693  
 Moeng, Letumile R 533  
 Mofenson, Lynne 584, 587  
 Moffatt, Kurtis 377  
 Moffitt, Richard 103  
 Mogno, Ilaria 219  
 Mohammadi, Abbas 276  
 Mohammed, Saira 709  
 Mohapi, Lerato 130, 559  
 Mohlale, Amanda 675  
 Mohr, Raphael 455  
 Moineddin, Rahim 484  
 Moir, Susan 273, 299  
 Mokhele, Kuena 400  
 Molale, Robert 675  
 Moldt, Brian 220, 425  
 Molefi, Mooketsi 645  
 Molina, Jean-Michel 148, 416, 419  
 Molina-Arana, David 619  
 Mollema, Femke P N 695  
 Molsberry, Samantha A 338  
 Molto, Jose 161  
 Momper, Jeremiah 607  
 Monaco, Daniel 275  
 Mondini, Annalisa 336, 545  
 Monje, Olivia Muñoz 308  
 Monroe, Anne 533, 643  
 Monroe-Wise, Aliza 446  
 Montaner, Julio S G 628, 663, 664, 709  
 Montaner, Luis J 156  
 Montanha, Maiara Camotti 374, 377, 378, 606  
 Montefiori, David 257, 268, 583, 618  
 Monteiano, Rocio 534, 535  
 Montes, Maria Luisa 453, 460  
 Montiel-Garcia, Daniel J 434  
 Montoya, Vanessa R 81  
 Montrond, Maureen 364  
 Moodley, Dhaya 587  
 Moodley, Pravikrishnen 95  
 Moody, M Anthony 625  
 Moon, Jee-Young 247  
 Moore, Ayana 678, 680, 682  
 Moore, David 628, 776  
 Moore, David J 327, 328, 331, 711, 713  
 Moore, Kelvin L 762  
 Moore, Mia 735  
 Moore, Richard 102, 104, 275, 409, 410, 411, 456, 468, 565, 654, 671, 734  
 Moosa, Mahomed-Yunus 95, 263, 399, 563, 564, 661  
 Mora, Ricardo 653  
 Moragrega, Angela B 453  
 Moraleda, Cinta 619, 620  
 Morales, Ayana 169  
 Morales, Dariana 350  
 Moran, Caitlin A 247, 547  
 Moran, Laura 178, 498  
 Morand-Joubert, Laurence 419  
 Morano, Luis 413, 441, 469  
 Morcilla, Vincent 314  
 Moreau, Yvetane 599  
 Moreira, Joanna 562

- Morelli, Gaetano 364  
 Morenilla, Sandra 362  
 Moreno Fornés, Sergio 405  
 Moreno, Santiago 413, 443, 460, 527, 544, 549  
 Moreno, Victoria 453, 460  
 Moreno-Zamora, Ana María 460  
 Morgan, Ethan 666  
 Morgello, Susan 101, 342, 344  
 Mori, Hiroshi 302  
 Morin, Renaud 78  
 Morlat, Philippe 570  
 Morris, Alison 116  
 Morris, Sheldon 711, 713  
 Morrison, Charles 152, 275, 681  
 Morroni, Chelsea 571, 588  
 Morrow, Kristen N 157  
 Morrow, Mary 92, 354, 355  
 Morshed, Muhammad 709  
 Moser, Carlee B 396, 528, 529, 555  
 Mota Prego Rosmaninho, Pedro 205  
 Mothe, Beatriz 161  
 Motosoane, Tsietsjo 761  
 Motsomi, Kegaguetse P 133  
 Motta, Ilaria 371  
 Mouhim, Hannane 148  
 Mounzer, Karam 156, 406, 503  
 Moussa, Adel 364  
 Moussa, Charbel 168  
 Mouton, Hannes 662  
 Mowery, Danielle L 642  
 Moxley, Richard T 337  
 Moyana, Calvin 749  
 Moye, Jack 605  
 Moyle, Graeme 503  
 Moyo, Sikhulile N 590  
 Moysi, Eirini 273  
 Mozaffari, Essy 397  
 Mphande, Misheck 181  
 Mubiana-Mbewe, Mwangelwa 600  
 Muchengeti, Mazvita 479, 485, 610  
 Mudvari, Prakriti 299  
 Muehlbauer, Michael J 612  
 Mueller Johnson, Megan 603  
 Mueller, Yvonne 124  
 Muench, Jan 112, 213  
 Mugambi, Mary 427  
 Mugambi, Melissa 111  
 Mugavero, Michael 105  
 Mugerwa, Henry 94  
 Mugo, Nelly Rwamba 152, 721, 722  
 Muhairwe, Josephine 400, 431, 615  
 Muir, Luke 120  
 Mukandavire, Christinah 733  
 Mukanyimi, Bosco 477, 679  
 Mukerji, Shibani 307  
 Mukonda, Elton 647  
 Mukui, Irene 427  
 Mulatu, Mesfin 702  
 Muldoon, Eavan G 231, 742  
 Mulenga, Fredah 645  
 Mulenga, Lloyd 759  
 Müller, Janis 213  
 Muller, William 617  
 Mulligan, Kathleen 366, 367  
 Mulligan, Mark 119, 121  
 Mullin, Shelby 706  
 Mullins, James I 284  
 Mulwa, Edwin 635  
 Mun, Sung Soo 169  
 Muñoz, Cecilia 216  
 Munoz, Flor 617  
 Muñoz-Chapulí, Mar 581  
 Muñoz-Fernández, María Ángeles 269, 597  
 Munro, Cynthia 338  
 Muntanga, Veronica 143  
 Muresan, Petronella 604, 608  
 Murnane, Pamela 569, 635  
 Murray, Bernard 294  
 Murry, Jeffrey 294  
 Murthy, Srinivas 372  
 Musaazi, Joseph 90, 94  
 Musick, Beverly 509  
 Mussa, Aamirah 588  
 Mussini, Cristina 748  
 Mustanski, Brian 221  
 Musumari Masika, Patou 658  
 Mutambanengwe-Jacob, Mercy Tapiwa 567, 569  
 Mutetwa, Tinaye 166, 473  
 Muthoga, Charles 645  
 Muthumani, Kar 282  
 Muvunyi, Claude M 761  
 Muyindike, Winnie 95, 180, 399, 509, 565  
 Mvududu, Rufaro 149  
 Mwamba Zulu, Failes 679  
 Mwandumba, Henry 491  
 Mwanga-Amumpaire, Juliet 180  
 Mwangi, Jonathan 143  
 Mwangi, Joseph 356  
 Mwango, Albert 477, 679  
 Mwangwa, Florence 151  
 Mwansa, Muya 768  
 Mwape, Humphrey 579  
 Mwape, Sabe 679  
 Mweebo, Keith 679  
 Mweemba, Aggrey 759  
 Mwelase, Noluthando 178  
 Mwenechanya, Mpande 768  
 Mwendha, Rhoda M 729  
 Mwingeli, Nancy 707, 710  
 Myer, Landon 93, 149, 175, 183, 398, 568, 574, 647  
 Myers, Timothy G 236
- N-**  
 Nabisere, Ruth 90  
 Nabukalu, Doreen 720, 725  
 Nagashima, Kunio 79  
 Naggie, Susanna 135  
 Nahid, Payam 130, 561  
 Naidoo, Dhirisha 749, 750  
 Naidoo, Kogieleum 559  
 Naidoo, Nireshni 749  
 Naidoo, Pren 134  
 Naik, Vidula 128  
 Nair, Govind 318  
 Nair, Suma 703  
 Najjengo, Marjorie Sserunga 758  
 Nakagawa, So 113  
 Nakalema, Shadia 368  
 Nakamura, Mari 617  
 Nakasujja, Noeline 341  
 Nakatudde, Irene 175  
 Nakawooya, Hadijja 659  
 Nakayiwa, Frances 176  
 Nakazawa, Masato 248, 288  
 Nakigozi, Gertrude F 341, 720, 725, 763  
 Nakijoba, Ritah 368  
 Nakisige, Carol 474  
 Nakityo, Rose Bosa 758  
 Nalinya, Elizabeth 565  
 Nalugoda, Fred 659, 720, 725, 763  
 Nalukwago, Sophie 497  
 Nalumansi, Aminah 690  
 Namasopo, Sophie 592  
 Namayanja, Grace 729, 758  
 Namirembe, Constance 474  
 Nance, Robin M 98, 409, 468, 543  
 Nandakumar, Bharat 407  
 Nanditha, Ni Gusti Ayu 663, 664  
 Nanche, Denise 660, 767  
 Nansera, Denis 180  
 Nansereko, Brendah 763  
 Napravnik, Sonia 409, 410, 411, 543, 626  
 Naqvi, Asma 116  
 Naranatt, Pramod 692  
 Narayanan, Elisabeth 86  
 Narpala, Sandeep 160  
 Nash, Denis 109, 637, 699, 765  
 Nassel, Ariann 105  
 Nastouli, Eleni 596  
 Nasuuna, Esther M 729  
 Natarajan, Madhuri 724  
 Natesampillai, Sekar 189, 295  
 Nath, Avindra 299, 318, 345  
 Navarro, Antonio 159, 413  
 Navarro, Jordi 207, 306, 441  
 Navarro, María Luisa 581, 597, 616  
 Navarro, Marta 641  
 Nazzinda, Rashidah 497  
 Nazziwa, Esther 173  
 Nchioua, Rayhane 112  
 Ndagije, Felix 761  
 Ndhlovu, Lishomwa 219, 238, 323, 333, 528, 529, 672  
 Ndlazi, Bandile 675  
 Ndoadougme, Aude 511  
 Ndung'u, Thumbi 524  
 Ndyanabo, Anthony 659  
 Neary, Megan 379  
 Neaton, James 492  
 Nedelman, Jerry 562  
 Neesgaard, Bastian 488  
 Negron, Cristhian 350  
 Neilan, Anne M 150  
 Neish, Andrew S 583  
 Nekhai, Sergei 197, 198, 230  
 Nelson, Gard 388  
 Nelson, Jeffrey 726  
 Nelson, Kristen 636, 638  
 Nematadzira, Teacler Gamuchirai 176, 569  
 Neto, Eduardo Forleo 123  
 Nevado, Julián 534  
 Newcomb, Craig W 136  
 Neyens, Martine 403  
 Neyts, Johan 387  
 Ng, Kevin W 120  
 Ngidi, Julia 645  
 Ngo, Thomas 165  
 Ngobese, Hope 754  
 Ngobese, Nompumelelo 769  
 Ngubane, Nosipho 562  
 Ngubane, Thulani 755  
 Ngure, Kenneth 721, 722  
 Nguyen, Maggie 612  
 Nguyen, Minh Ly 547  
 Nguyen, Nadia 398  
 Nguyen, Quang N 193  
 Nguyen, Thi Thuy Van 446  
 Nguyen, Thuy 255  
 Nguyen, Trong-Tuong 490  
 Nguyen, Tung X 381  
 Nhampossa, Tacita 660  
 Niazi, Kayvan 272, 388  
 Nicastrì, Emanuele 545  
 Nichols, Brooke 181, 691, 766, 768  
 Nichols, Lisa 740  
 Nichols, Sharon L 593  
 Nicolau, Ioana 484  
 Nidadavolu, Lolita S 536  
 Nielsen, Jonas Bille 502  
 Nielsen, Susanne Dam 499, 502, 532  
 Nielsen-Saines, Karin 580  
 Niessl, Julia 303  
 Nijhawan, Ank 104, 685  
 Nijirazana, Bonaparte 186  
 Nikanjam, Mina 607  
 Nikoi, Kotey 759  
 Nikolaitchik, Olga 190  
 Nirula, Ajay 121, 122  
 Nishimura, Yoshiaki 82  
 Nishiura, Kenji 297, 714  
 Niu, Xin 352, 353, 355  
 Niubo, Jordi 358, 362  
 Nixon, Douglas 197, 230  
 Njindam, Iliassou Mfochive 733  
 Njuguna, Irene 558  
 Nkambule, Rejoice 649  
 Nkangana, Nontando S 171  
 Nkhoma, Harrid 746  
 Nkomo, Bornapate 590  
 Noce, Giuseppe 335  
 Noe, Amy T 271  
 Nonyane, Bareng AS 134  
 Noor, Syed W 776  
 Nordstgaard, Børge 499  
 Nordqvist Kleppe, Sara 476  
 Nori, Achyuta 142  
 Norman, Jennifer 93  
 Norris, Philip 310  
 North, Crystal M 495  
 Norton, Chasity 728  
 Norwood, Jamison 726  
 Notari, Stefania 242  
 Nouhin, Janin 423, 435, 436  
 Nouraie, Mehdi 230  
 Novak, Richard 121, 504  
 Novella Mena, María 339  
 Novik, Laura 160  
 Nozyce, Molly 593  
 Nsakala, Bienvenu Lengo 400, 431  
 Nsofwa, Dailes 679  
 Ntinga, Xolani 111  
 Nugent, Joshua R 151  
 Nuñez, Mar 619  
 Nunn, Amy S 700  
 Nussenzweig, Michel 146  
 Nuttall, Jeremy 147  
 Nyakato, Patience 615  
 Nyandiko, Winstone 612  
 Nyathi, Siphso 134  
 Nyirenda, Godwin 600  
 Nyirenda, Rose 585, 746  
 Nzuzza, Mpilonhle 769
- O-**  
 O'Connor, Catherine 617  
 O'Meara, Matthew J 187  
 Oberholzer, Michael 343  
 Obernier, Kirsten 187  
 Oboho, Ikwo 738  
 Obregon-Perko, Veronica 83, 204, 296, 621  
 O'Brien, Julie 100  
 O'Brien, Meagan P 123  
 O'Broin, Cathal 96  
 Ocampo Hermida, Antonio 401  
 Ochieng, Ben 707, 710  
 O'Connor, Eileen 742  
 O'Connor, Patrick 683  
 Odayar, Jasantha 93, 647  
 O'Dell, Sijy 273  
 Odhiambo, Albert M 635  
 Odhiambo, Francesca 635  
 Odinga, Daniel 710  
 Oele, Elizabeth 560  
 Ofner, Susan 509  
 Ofotokun, Igbo 512, 526, 538, 547  
 Ogbe, Ane 158  
 Ogbuagu, Onyema 395  
 Ogollah, Francis M 634  
 Ogwu, Anthony 568  
 OhAinle, Molly 81, 292  
 O'Halloran, Jane 516  
 Ohayon, Michel 148  
 Okeke, Nwora Lance 506, 673, 773  
 Okello, Samson 495  
 Okere, Nwanneka 767  
 Okhai, Hajra 727  
 Okoche, Lazarus 474  
 Okochi, Hideaki 354, 355, 569, 699, 710  
 Okulicz, Jason 483  
 Okwero, Margaret A 725  
 Olago, Victor 479, 485, 610  
 Olalla, Julián 641  
 Olefsky, Maxine 91  
 Olender, Susan 393  
 Olex, Amy L 103, 141  
 Olivares, Isabel 226  
 Oliver, Danielle 204  
 Oliver, Nora 547  
 Oliveto, Giuseppe 208, 266  
 Olivier, Jacobus 173  
 Olivier, Stephen 524  
 Olivier, Susanna E 171  
 Olsen, Margaret 516  
 Olson, Anders 388  
 Olugbosi, Morounfolu 562  
 Oluoch, Lynda Myra 721, 722  
 Oliveira, Antonio 453, 460  
 Olvera, Alex 264  
 Omodi, Victor 743  
 Omoding, Daniel 399  
 Omondi, Fredrick Harrison 283  
 Omoz-Oarhe, Ayotunde 178  
 Onaga, Chuka 756  
 Onyango, Clayton 635  
 Onyango, Dickens Otieno 560  
 Opekun, Antone 464  
 Opoka, Robert O 592  
 Opoku, Jenevieve 643  
 Opollo, Valarie 435  
 Oprea, Cristiana 414

- Orem, Jackson 474  
 Orkin, Chloe 414, 415, 416, 505  
 Orlando, Silvia 335  
 Orrell, Catherine 175, 371, 398, 662  
 Orti, Joaquin-Amat 405  
 Ortiz Barquero, María Concepción 616  
 Ortiz, Alexandra 201, 279  
 Ortiz, Raquel 226  
 Osborn, Matthew 155  
 O'Shea, Callan 342  
 Osinusi, Anu O 395  
 Osman, Nathan 651  
 Oster, Alexandra M 688  
 Ostrenga, Lauren 105  
 Ostrowski, Sisse Rye 532  
 Otaalo, Brian 90  
 Otis, Joanne 651  
 O'Toole, Riley 321  
 Ottaway, Zoe 508  
 Ottogalli, Paolo 242  
 Ottou, Sandrine 334  
 Otvos, James 324  
 Ouchi, Dan 210, 264, 281  
 Ounchanum, Pradthana 604  
 Overbaugh, Julie 261  
 Overton, E Turner 401, 494, 496, 498, 505, 506, 518  
 Owczarzak, Jill 770  
 Owen, Andrew 379  
 Owen, Leah 645  
 Owor, Maxensia 587  
 Owuoth, John 557, 732  
 Owusu, Samuel 236  
 Oxenford, Sally 233  
 Oyebanji, Oyebola 749  
 Oyungu, Eren 591
- P-**  
 Pace, Craig 425  
 Pace, Matthew 158  
 Pacheco Garcia, Vinicius 493  
 Pacheco-López, Yolanda María 235  
 Pacis, Caitleen 288  
 Padgett, Denis 510  
 Padilla, Giune 117  
 Padmanabhan Chandrasekar, Aswath 189, 295  
 Pagliari, Matteo 624  
 Pagliuzza, Amélie 154, 298, 303  
 Pahwa, Rajendra 245, 246, 286  
 Pahwa, Savita G 245, 246, 260, 286  
 Paiardini, Mirko 118, 277  
 Painter, Wendy P 777  
 Palacios, Rosario 445, 469  
 Palanee-Phillips, Thesla 716  
 Palau, Vansea 206  
 Palefsky, Joel 168  
 Palella, Frank 338, 504, 518, 526, 538, 752  
 Palfreeman, Adrian 142  
 Pallikkuth, Suresh 245, 246, 260, 286  
 Pallin, Maria 260  
 Palm, David 418  
 Palma, Paolo 172, 245, 246, 286, 596, 598, 622  
 Palmer, Clovis S 114, 156  
 Palmer, Sarah 301, 314  
 Palmer, Steven 630  
 Palmieri, Fabrizio 545  
 Pals, Sherri L 738  
 Paltiel, David 150, 771  
 Pampana, M Betina 277  
 Panczak, Radoslaw 139  
 Pandey, Janardan P 160  
 Pandey, Kabita 382  
 Pandey, Urvashi 239, 252  
 Pang, Alina 528  
 Pankam, Tippawan 179  
 Panneer, Nivedha 676  
 Pantaleo, Giuseppe 308  
 Paolillo, Emily W 328  
 Papisavvas, Emmanouil 156  
 Papazova, Natalia 390  
 Pape, Jean W 184, 185, 510  
 Pappa, Keith A 417  
 Parcesepe, Angela 637  
 Parczewski, Milosz 443  
 Pardons, Marion 154, 215  
 Paredes, Roger 259, 265, 412, 429  
 Pareek, Manish 142  
 Pareja, Marta 581, 616  
 Parikh, Ajay 557, 732  
 Parikh, Urvi 427, 428  
 Parisi, Saverio Giuseppe 693  
 Park, Eun Young 323  
 Park, Lesley S 478, 626  
 Parker, Robert A 769  
 Parman, Mariel 105  
 Parolini, Lucia 158  
 Parruti, Giustino 137  
 Parry, Sarah 684  
 Parsons, Elizabeth 155  
 Parvangada, PC 425  
 Pasalar, Sivash 252, 287  
 Pascoe, Rachel 280  
 Pascom, Ana Roberta Pati 741  
 Pascual, Julio 206  
 Pascucci, Giuseppe R 172, 622  
 Pasquazzi, Caterina 137  
 Pasyar, Sarah 604  
 Patel, Dipak R 122  
 Patel, Eshan U 447, 681  
 Patel, Foramben 302  
 Patel, Munjal 87  
 Patel, Nimeshkumar 656  
 Patel, Parul 505  
 Patel, Rena 103, 109, 141, 553, 743  
 Patel, Roosheel 388  
 Patenaude, Bryan 745  
 Pathak, Vinay K 79, 190  
 Pathela, Preeti 699  
 Paton, Nicholas 94  
 Patro, Sean 299  
 Patterson, Thomas L 652, 663  
 Paudel, Misti L 525  
 Paul, Kavuma 729  
 Paul, Robert 163, 164, 317, 323, 333, 340, 341, 672  
 Paulsen, Chane 171  
 Payne, Daniel 634  
 Paz, Paula 660  
 Pearson, Catherine 762  
 Pedersen, Jannie 267  
 Pedreño-López, Sònia 206  
 Pea, Ritumetse 400  
 Peer, Cody 167  
 Peet, M Melissa 715  
 Pegu, Amarendra 82  
 Pei, Luxin 243  
 Pei, Pamela 670  
 Pekosz, Andrew 209  
 Pellegrino, Pierre 262  
 Pelletier, Adam 281  
 Pelletier, Adam Nicolas 215  
 Peloakgosi-Shikwambani, Keneilwe 689  
 Peluso, Michael A 627  
 Pena Dias, Jenny 458  
 Peña, Ruth 210, 265, 281  
 Penazzato, Martina 444  
 Penchala, Sujana D 358, 361  
 Pene Dumitrescu, Teodora 126  
 Penner, Murray 418  
 Peppia, Dimitra 262  
 Peraire, Joaquin 194, 405  
 Perea, David 207, 386  
 Pereira Ribeiro, Susan 84, 118, 215  
 Pereira, Gerson Fernando Mendes 741, 771  
 Pereira, Isabela Ornelas 741  
 Perelson, Alan S 125  
 Peretti, Delphine 570  
 Perez Irizarry, Javier 481  
 Pérez Pérez, Alba 616  
 Pérez Yanes, Silvia 226  
 Perez, Jaime A 548  
 Perez, Katherine K 393  
 Pérez, Liliana 299, 304, 345  
 Perez-Brumer, Amaya 530  
 Pérez-Elias, María Jesús 417, 549  
 Perez-Gomez, Alberto 194, 224  
 Pérez-Moneo, Begoña 619  
 Pérez-Seoane, Beatriz 581, 616  
 Perez-Valero, Ignacio 339, 453, 460  
 Perisa, Damir 139  
 Perłowski, Charlotte 608  
 Permar, Sallie 618  
 Permar, Sallie R 83, 296, 625  
 Pernas, Maria 226  
 Perno, Carlo Federico 429, 748  
 Perreau, Matthieu 308  
 Perrier, Trevor 566  
 Perry, Leslie 684  
 Person, Anna 565  
 Perte, Mihaela 305  
 Pertine, Henry 379  
 Peruski, Anne H 676, 688  
 Peters, Brandilyn A 247  
 Peters, Helen 586  
 Peters, Lars 443, 452  
 Peters, Marion 467  
 Petersen, Kalen 317  
 Petersen, Maya L 151  
 Peterson, Marc 578  
 Petrara, Maria Raffaella 172, 622, 623, 624  
 Petrosillo, Nicola 545  
 Petrovas, Constantin 273  
 Petsis, Danielle T 723  
 Pett, Sarah L 508  
 Pettit, April 130  
 Peykov, Victor 272  
 Peytavin, Gilles 511, 570  
 Pham, Michael Huy Cuong 499  
 Pham, Michelle 368  
 Pham, Phuong 424  
 Phanuphak, Nittaya 154, 163, 179, 323, 340, 407, 408, 672  
 Philibert, Patrick 126  
 Philip, Goulder 158  
 Philip, Neena M 152, 649  
 Phillips, Patrick Peter John 130  
 Phillips, Tamsin Kate 93, 183, 647  
 Phiri, Bevis 768  
 Phiri, Martin 477  
 Phiri, Sam J 615  
 Phongsamart, Wanatpreeya 601  
 Phothidokmai, Charnnarong 370  
 Pialoux, Gilles 148  
 Pickel, Julia 723  
 Pickering, R Taylor 514  
 Picone, Olivier 582  
 Pierangeli, Alessandra 208, 470, 472  
 Piermatteo, Lorenzo 137  
 Pierret, Chloe 454  
 Pietersen, Ismelda 143  
 Pieterse, Nadia 640  
 Pietropaolo, Keith 364  
 Piggott, Damani A 458, 536  
 Pike, Steven 684  
 Pillai, Satish 234, 310  
 Pillay, Azure-Dee AP 361  
 Pillay, Deenan 399, 524  
 Pimenta, Cristina 771  
 Pinacchio, Claudia 208, 470, 472  
 Pineda, Juan A 445, 466, 469  
 Pines, Heather A 652  
 Pinho, Rosana Elisa Gonçalves 741  
 Pinilla, Mauricio 587  
 Pinnetti, Carmela 334, 336, 545, 748  
 Pino, Maria 118  
 Pinsky, Benjamin A 423, 436  
 Pintado, Claire 148  
 Pinto, Daniel 249  
 Pinto, Jorge 614  
 Pinto-Martinez, Adriana 339  
 Pinto-Santini, Delia M 239, 287  
 Pintye, Jillian 707, 710  
 Pinyakorn, Suteeraporn 154, 179, 340, 359, 407, 408  
 Pipper, Jeanna 147  
 Pipkin, Sharon 730  
 Pirriatore, Veronica 335  
 Pisa, Pedro 182  
 Pisanic, Nora 209  
 Piscitelli, Joseph 607  
 Piselli, Pierluca 242  
 Pitasi, Marc A 739  
 Pittillides, Paris 756  
 Pittaluga, Stefania 480  
 Piwowar-Manning, Estelle Marie 153, 682  
 Plana, Montserrat 228, 412  
 Planas, Bibiana 306  
 Planas, Delphine 233  
 Planelles, Vicente 159, 290  
 Plank, Rebecca M 87  
 Plankey, Michael 538, 539  
 Plantier, Jean-Christophe 404  
 Plata, Marta 619  
 Plaza-Jennings, Amara 342  
 Plazzi, Maria Maddalena 334  
 Pleasure, Samuel 165  
 Pleet, Michelle 249  
 Plinkton, Mark 311  
 Plückthun, Andreas 85  
 Podany, Anthony T 91  
 Podlaha, Ondrej 220  
 Podzameczer, Daniel 256, 358, 362, 412, 413, 549  
 Polak, Paz 166  
 Polakowski, Laura 257  
 Polisen, Amanda 356  
 Polizzotto, Mark N 492  
 Pollard, Katherine 310  
 Pollard, Rose 145, 745  
 Polli, Joseph W 402, 505, 541  
 Poltavee, Kultida 163, 179  
 Polyak, Christina 519, 557, 732  
 Pomputius, William 617  
 Ponticciello, Matthew 180  
 Porrachia, Magali 692  
 Porteiro, Norma 414  
 Porter, Sarah 143  
 Portilla, Joaquín 413  
 Post, Frank A 508, 540  
 Post, Wendy 324  
 Poteat, Tonia 657  
 Pothisri, Mantana 163  
 Potlapalli, Sindhu 583  
 Pourcher, Guillaume 511  
 Pourcher, Valérie 511  
 Poveda, Eva 227  
 Powderly, William 516  
 Powis, Kathleen M 573, 575, 590, 609  
 Prabhakaran, Madhu 86  
 Pradenas, Edwards 256, 259  
 Pradhan, Suman 462  
 Prado, Julia G 210, 264, 265, 281  
 Prajapati, Girish 525  
 Prasad, Sonya 486  
 Prata Menezes, Neia 719  
 Prelli Bozzo, Caterina 112, 213  
 Premeaux, Thomas Alan 528, 529  
 Pretorius Holme, Molly 609  
 Price, Colleen 484  
 Price, David A 279  
 Price, Jennifer 456  
 Price, Joan T 578, 579  
 Price, Richard 349  
 Prieto, Paula 159, 256, 358  
 Procopio, Francesco Andrea 308  
 Protack, Tricia 421  
 Prozesky, Hans 662  
 Prueksakaew, Peeriya 359, 407  
 Pry, Jake 600  
 Psaros, Christina 713  
 Pugliese, Pascal 537  
 Puglisi, Elisabetta V 423  
 Puglisi, Joseph D 423  
 Pujato, Mario 351  
 Pujol, Joan Miquel 620  
 Pujol-Gimeno, Aleix 210, 264  
 Pulido, Federico 414  
 Pung, Leland 773  
 Puoti, Massimo 748  
 Puray-Chavez, Maritza N 188  
 Purcell, David 704  
 Puren, Adrian 757  
 Purpura, Lawrence 212, 554  
 Purswani, Murli 603  
 Puthanakit, Thanayawee 595  
 Pye, Valerie E 120
- Q-**  
 Qasmieh, Saba 699  
 Qavi, Ambar 572  
 Qiu, Ju 195  
 Queiroz, Artur T L 559

- Quinn, Thomas 321, 341, 447, 681, 690  
 Quirant, Bibiana 210, 264
- R-**
- Rabie, Helena 605  
 Rabizadeh, Shahrooz 272, 388  
 Raboisson, Pierre 387  
 Raboud, Janet 568  
 Raccamarich, Patricia 260  
 Radix, Asa 107  
 Radtchenko, Janna 503  
 Rae, Caroline 162  
 Raedeker, Lukas 633  
 Raffi, François 537  
 Rafful, Claudia 652  
 Ragsdale, Amy 221  
 Rahangdale, Lisa 168  
 Rahman, Adeeb 211  
 Rahman, Gibraan 348  
 Rahman, Sheikh Abdul 157  
 Raho Mousa, Mariem 537  
 Rai, Mohammad A 351  
 Raizes, Elliot 761  
 Rajap, Shuabe 750  
 Rakhit, Roby D 550  
 Rakuoane, Itumeleng 400  
 Ramaswami, Ramya 167, 170, 475, 480  
 Ramesh, Divya 123  
 Ramgopal, Moti 220, 503  
 Ramogola-Masire, Doreen 571  
 Ramos, Artur 435  
 Ramos, José Tomás 597  
 Ramos-Roure, Francesc 210  
 Rana, Aadia 105  
 Rana, Sohail 230  
 Randhawa, April 257  
 Randhawa, Bally 294  
 Rane, Madhura S 637  
 Rangel, Gudelia 652  
 Rannard, Steve 379  
 Ransby, Imani 726  
 Ransier, Amy 192, 193, 279  
 Rao, Darcy 755  
 Rao, Shubha 702  
 Rapala, Alicia 491  
 Rasmussen, Line D 443  
 Rasmussen, Thomas A 280, 301  
 Rassadkina, Yelizaveta 225, 286, 307  
 Ratsela, Andrew 133  
 Rauch, Andri 449, 450, 452, 457  
 Rausch, Jason W 639  
 Rautenberg, Tamlyn 95  
 Rautiainen, Susanne 658  
 Ravel, Jacques 579  
 Raventós, Berta 306, 405  
 Ravindra, Neal 287  
 Rawlings, Stephen A 248, 288, 692  
 Rawson, Jonathan 190  
 Raychaudhury, Suchismita 471  
 Raymond Marchand, Laurence 233  
 Read, Lucy 175  
 Real, Luis M 224, 445, 466, 469  
 Rebeiro, Peter F 510  
 Redd, Andrew 681  
 Reddy, Krishna P 670  
 Rees, Helen V 152, 158  
 Rees-Spear, Chloe 120  
 Regan, James 276  
 Reglero, Cristina 227  
 Rehm, Catherine 222, 255  
 Reich, Daniel 318  
 Reid, Giles 634  
 Reidy, Jason 115  
 Reilly, Cavan 492  
 Reinberg, Thomas 85  
 Reirden, Daniel 366, 367, 603  
 Reisner, Sari 530  
 Reiss, Peter 237  
 Remeeva, Jenny 390  
 Remien, Robert 398  
 Ren, Yanqin 305  
 Rentsch, Christopher T 104, 454  
 Reoma, Lauren B 299, 345  
 Resino, Salvador 549  
 Reyes-Teran, Gustavo 251, 273  
 Reyes-Uruña, Juliana 405
- Reynders, Tom 88  
 Reynolds, Helen 175  
 Reynolds, Jessica L 346  
 Reynolds, Steven 659, 725  
 Reynolds, Steven J 341, 690  
 Rezeli, Veronica V 187  
 Rhee, Elizabeth G 376  
 Rhee, Martin 89, 127, 128  
 Rhee, Soo-Yon 433  
 Rhodes, Ajantha 280, 301  
 Riaza, Monica 581, 616  
 Ribaud, Heather J 494, 496, 498, 506  
 Ribeiro, Ruy M 125  
 Ribera, Esteve 413  
 Rice, Adrian 272  
 Rice, Michelle 513  
 Richardson, Barbra A 427, 566, 577, 707  
 Richardson, Lynne D 683  
 Richardson, Peter 471  
 Richmond, Gary 127, 401  
 Richter, India 221  
 Ridolfi, Marco 470  
 Riera, Marta 206  
 Rijnders, Bart J A 124, 391, 392, 695  
 Rinaldi, Stefano 245, 246, 286  
 Rinaldo, Charles 241  
 Rincon, Pilar 466  
 Rinehart, Alex R 153  
 Ring, Kyle 142  
 Ringheim, Hedda 532  
 Rinke de Wit, Tobias 767  
 Ríos, María José 469  
 Riou, Julien 139  
 Ripamonti, Diego 393  
 Rittenhouse, Katelyn J 579  
 Ritz, Justin 396, 555  
 Rivadeneira, Emilia 173  
 Riveira-Muñoz, Eva 206  
 Rivera, Christina G 380  
 Rivero, Angel 161  
 Rivero, Antonio 469  
 Rivero-Juarez, Antonio 445  
 Riviere, Cynthia 184  
 Rizza, Stacey A 380  
 Rizzardini, Giuliano 126, 401  
 RM Almeida, Afonso 205  
 Roach, Margaret Eyerman 260  
 Roan, Nadia 247, 310  
 Robb, Merlin 154, 595  
 Robbins, Gregory 135  
 Robbins, Reuben N 398  
 Roberts, Allen 648, 755  
 Robertson, McKaylee M 637  
 Robertson, Michael N 87, 88  
 Robine, Nicolas 253  
 Robinson, Nicola 158  
 Robson, Isabella 181  
 Rocco, Joseph 170, 243  
 Rockstroh, Jürgen K 439, 442, 443, 452, 455, 686  
 Rockx, Barry 124  
 Rodes, Berta 534, 535  
 Rodrigues, Warren 354  
 Rodríguez De La Concepción, María Luisa 259  
 Rodriguez, Elaine 350  
 Rodríguez-Barradas, María 478  
 Rodríguez-Benitez, Rosa J 333  
 Rodríguez-Centeno, Javier 534, 535  
 Rodríguez-Hart, Cristina 107  
 Rodríguez-Molino, Paula 620  
 Roederer, Mario R 160  
 Roger, Michel 651  
 Rogers, Denise A 271  
 Rogers, Kai 389  
 Rogers, Rodney 467  
 Roh, Meejeon 229  
 Rohner, Eliane 479, 485, 610  
 Rojas Castro, Daniela 148  
 Rojo, Pablo 596, 597  
 Rojo, Pablo 617  
 Rokx, Casper 124, 391, 392, 695  
 Romero, Luis 264  
 Romero, MP 619  
 Romney, Marc 709  
 Romo, Matthew L 109
- Ron, Raquel 527  
 Ronen, Keshet 566, 577  
 Ronit, Andreas 532  
 Rooney, James F 153  
 Rorie, Michele 702  
 Rosa, Annachiara 120  
 Rosado, Joel 207, 386  
 Rosado-Sánchez, Isaac 235  
 Rosas, Marta 460  
 Rose, Burt 422  
 Rosen, Elias 356, 357  
 Rosen, Sydney 764, 766, 768  
 Rosenberg, Eli 706  
 Rosenberg, Eric Scott 155, 309  
 Roskin, Krishna 351  
 Rossenu, Stefaan 403  
 Rossi, Paolo 172, 596, 622  
 Rostad, Christina A 621  
 Roth, Mark J 480  
 Rothenberg, Rich 636, 638  
 Rothenberger, Sylvia 385  
 Rothman, Richard 683, 690  
 Rottey, Sylvie 88  
 Rougvié, Miguel De Mulder 197, 230  
 Rousseau, Kimberly E 217  
 Rouster, Susan D 462  
 Routh, Andrew L 434  
 Routhu, Nanda K 583  
 Routy, Jean-Pierre 233, 298, 303, 651  
 Roviro, Carla 226  
 Rowan, Sarah E 546  
 Rowe, William 717  
 Rowland-Jones, Sarah 262  
 Roxby, Alison C 721, 722  
 Roychoudhury, Pavitra 138  
 Royle, Kathryn 471  
 Rozen, Elliot 699  
 Ruane, Peter J 127  
 Rubin, Leah 101, 321, 322, 324, 337, 341  
 Rubinstein, Paul 169  
 Ruczinski, Ingo 275  
 Rudnicki, Erika 718  
 Ruffieux, Yann 485, 662  
 Ruffoni, Elena 623  
 Ruggiero, Alessandra 172, 598, 622  
 Ruggio, Natalie 389  
 Ruiz, Rocío 224  
 Ruiz-Mateos, Ezequiel 194, 224, 227  
 Rull, Anna 194, 227  
 Ruone, Susan 714  
 Russo, Alessandro 470  
 Rutakingirwa, Morris 131  
 Ruwanpathirana, Anushka 214  
 Ryan, Pablo 339  
 Rybak, Rainer 686  
 Ryscavage, Patrick 451
- S-**
- Saad, Hadil 660  
 Saag, Michael 409  
 Saavedra-Lozano, Jesús 620  
 Sabin, Caroline 100, 508, 727  
 Sabo, Janelle 121, 122  
 Sabranski, Michael 439, 442  
 Sabrido, Gema 619  
 Sacco, Leonardo 343  
 Saccalán, Carlo 163, 179, 323, 340, 407, 408, 672  
 Sacha, Jonah 279  
 Sachatp, Karam 634  
 Sachs, Nancy A 129  
 Sacktor, Ned 101, 321, 337, 338, 341  
 Saduvala, Neeraja 688  
 Saeed, Sahar 448  
 Sáez, María 224  
 Safo, Sandra E 492  
 Safrif, Jeffrey T 272  
 Sagar, Manish 599  
 Saha, Pooja 578  
 Sahabo, Ruben G 186  
 SahBandar, Ivo 219, 323  
 Sahoo, Malaya K 423  
 Sahrman, John 516  
 Sahu, Maitreyi 755  
 Sailasuta, Napapon 163  
 Sainly, Giovanni 184
- Sainz, Talia 597  
 Saiz-Medrano, Gabriel 534, 535  
 Salahuddin, Syim 244, 481  
 Salami, Bukola Oladunni 592  
 Salazar, Ana 260  
 Salihi, Abdulsamad 736, 774  
 Saloner, Rowan 328  
 Salpini, Romina 137  
 Salters, Kate 484, 628, 664  
 Samaneka, Wadzanai 130  
 Samanovic-Golden, Marie I 119  
 Samarawickrama, Amanda 540  
 Samer, Sadia 277, 313  
 Samperiz, Gloria 544  
 Samuels, David 325, 459, 521, 522  
 Sanchez, Francisco 216, 269  
 Sanchez, Hugo 650  
 Sanchez, Travis 636, 638  
 Sanchez-Conde, Matilde 460  
 Sánchez-Gaona, Nerea 207  
 Sánchez-Luna, Manuel 581, 616  
 Sanders, Lisa 257  
 Sandlin, Rebecca 352, 353  
 Sanford, Daniel C 272  
 Sang, Jordan 776  
 Sang, Norton Mutai 635  
 Sanne, Ian 130  
 Sannier, Gérémy 303  
 Santamaria, Ulisses 299, 318, 345  
 Santana-Suarez, Beatriz 508  
 Santhanam, Anand 719  
 Santiago, Mario 218  
 Santiago, Steven 503  
 Santilli, Veronica 172  
 Santinelli, Letizia 208, 470, 472  
 Santoro, Maria Mercedes 429  
 Santos, Diana F 205  
 Santos, Jesús 441, 445  
 Santos, José Ramón 281, 429  
 Santos, Marta 469  
 Sanyal, Arun J 395  
 Sanz, Jesus 269  
 Sanz, Olga 581, 616  
 Sanza-Moreno, Jose 641  
 Sanz-Santaefumia, Francisco José 620  
 Saraceni, Valeria 556  
 Sarkar, Neena 123  
 Sarkar, Sanjay 384  
 Sarmati, Loredana 137  
 Sarnello, Daniele 233  
 Satija, Namita 302  
 Sato, Kei 113  
 Satre, Derek D 97, 330  
 Saumoy, María 256, 358, 412, 544  
 Saunders, Kevin 268  
 Sauter, Daniel 112, 113  
 Savarino, Andrea 313, 394  
 Savchuk, Nikolay 390  
 Savic, Rada 561  
 Savinelli, Stefano 258  
 Sawangsinth, Panadda 595  
 Sawyer, Aubrey 229  
 Sax, Paul E 176, 177, 415, 503  
 Saylor, Deanna 321, 338, 341  
 Scaggiante, Renzo 693  
 Scagnolari, Carolina 208, 266, 470, 472  
 Scarsi, Kimberly K 91, 368  
 Scevola, Sofia 256, 358, 362  
 Schaafsma, Torin T 111  
 Schacker, Timothy 359  
 Schade, Andrew E 121, 122  
 Schaison, Aurelie 307  
 Schalper, Kurt 481  
 Schekter, Rachel 604  
 Scheer, Susan 762  
 Scheinberg, David 169  
 Schell, Sonja 171  
 Scheuerle, Angela E 584  
 Schewe, Knud C 439, 442  
 Schim van der Loeff, Maarten 237  
 Schinazi, Raymond 118  
 Schiro, Faith 84, 199  
 Schlätzer, Daniela 490  
 Schlegel, Anja 385  
 Schlick, Kayla A 548

- Schlub, Timothy 274  
 Schmeisser, Hana 236, 271  
 Schmid, Patrick 449, 450, 457  
 Schmidt, Axel J 442  
 Schmidt, Haley 681  
 Schmidt, Stephen D 193  
 Schmitto, Coleton 762  
 Schneider, Katrin 139  
 Schnittman, Samuel R 98, 254  
 Schnure, Melissa 668, 775  
 Schoen, Patrick 703  
 Schofield, Christina 483  
 Scholte, Florine 267  
 Scholten, Stefan H A 417  
 Scholtes, Gael 229  
 Scholz, Erin M B 360  
 Schouten, Erik 585  
 Schrank, Travis P 188  
 Schriver, Emily R 642  
 Schubert, Oliver 686  
 Schumock, Grant 140  
 Schwab, Robert 88  
 Schwamm, Eli L 670  
 Schwartz, Robert P 683  
 Schwartz, Sheree 733  
 Schwarze-Zander, Carolynne 455  
 Sciarra, Francesca 208  
 Socca, Viviana 78  
 Sconza, Rebecca 586  
 Scordio, Mirko 208, 266, 472  
 Scott, Brianna 288, 692  
 Scott, Hyman 730  
 Scott, Justine 771  
 Scott, Megan 629  
 Scoville, Caitlin 152  
 Scully, Eileen P 140, 248, 288, 289, 461  
 Seaberg, Eric C 324, 338  
 Seaman, Michael 146, 276  
 Seaton, Kelly E 609  
 Sebastian, Jakob 633  
 Sebastiani, Giada 456  
 Sebra, Robert 302, 305  
 Secord, Elizabeth 603  
 Secours, Rode 185  
 Seeburg, Ulrike 431  
 Seedat, Soraya 662  
 Seeley, Janet 524, 753  
 Segal, Mark 99  
 Segal-Maurer, Sorana 127  
 Seiger, Kyra Weston 309  
 Seiphetlo, Thabiso B 361  
 Sekaggya-Wiltshire, Christine 90  
 Sékaly, Raïck-Pierre 82, 84, 118, 273, 281  
 Sekiziyiv, Arthur Brian 758  
 Selisho, Mirriam 477  
 Selke, Stacy 721, 722  
 Sellas, Anna 310  
 Sellers, Brian 237  
 Sembajwe, Sophie 108, 655  
 Semeere, Aggrey 486  
 Sendagala, Samuel 758  
 Sendak, Mark 773  
 SenGupta, Devi 161, 220, 312  
 Senserrich, Jordi 206  
 Sension, Michael 406  
 Seo, Yuna 236  
 Seoane, Javier 596  
 Seow, Jeffrey 120  
 Sequeria, Neil 185  
 Sereda, Paul 628  
 Serenata, Cécilia M 517, 572  
 Sereti, Irini 170, 237, 243  
 Serna-Pascual, Miquel 596, 620  
 Serrano, Anna 386  
 Serrano, Esther 466  
 Serrano, Miriam 469  
 Serrano-Villar, Sergio 527  
 Serrao, Claire 747, 749, 750  
 Serwadda, David 690  
 Serwanga, Jennifer 690  
 Sessa, Libera 598  
 Seurinck, Ruth 215  
 Sevenler, Derin 352, 353  
 Severe, Karine 185  
 Severe, Patrice 178, 184  
 Sewankambo, Nelson 725, 763  
 Sewe, Victor 435  
 Shafer, Robert W 423, 433, 435, 436  
 Shah, Jayesh 212, 332  
 Shah, Maunank 668, 775  
 Shah, Sarita 547, 654  
 Shah, Svati J 612  
 Shahid, Aniq 283, 432  
 Shahmanesh, Maryam 753  
 Shaikh, Maliha W 114  
 Shakil, Anika 379  
 Shakwelele, Hilda 768  
 Shalit, Peter 220  
 Shamim, Nakade 729  
 Shang, Judith 143  
 Shang, Zongbo 617  
 Shao, Wei 304, 639  
 Shao, Yongwu 438  
 Shapiro, Adrienne E 543  
 Shapiro, Lawrence 85  
 Shapiro, Roger 176, 286, 568, 571, 576, 588, 609  
 Sharaf, Radwa 437  
 Sharkey, Mark 260  
 Sharma, Amit 383  
 Sharma, Anjali 247, 538, 539, 667  
 Sharma, Ashish A 215, 273, 281  
 Sharma, Roshan 253  
 Sharma, Sunita 297  
 Sharma, Sunny 756  
 Sharp, Joanne 379  
 Sharpe, Alan 742  
 Sharpey-Schaefer, Kieran 764  
 Shauer, Amanda P 204  
 Shaw, George 83, 296  
 Shaw, Pamela A 642, 677, 723  
 Shaw, Renata M 512  
 Shazi, Zinhle M 769  
 Sheahan, Timothy 384, 777  
 Shebl, Fatma 478, 670, 771  
 Sheehan, Gerard 100, 231, 742  
 Sheehan, Nancy 372  
 Sheha, Irene 491  
 Shelly, Wang 157  
 Shen, Lei 121, 122  
 Shen, Nikki 734  
 Shen, Yanhan 332  
 Sheng, Wang-Huei 463  
 Shepherd, Bryan 510, 565, 726  
 Sherman, Brad T 195  
 Sherman, Jessica P 666  
 Sherman, Kenneth E 462  
 Sherr, Lorraine 589, 727  
 Sheth, Anandi N 512, 526, 547  
 Shiau, Stephanie 332  
 Shibemba, Aaron 679  
 Shigenaga, Judy K 98  
 Shiha, Gamal 446  
 Shikuma, Cecilia M 238, 333  
 Shimony, Joshua S 164  
 Shin, Annie 272, 388  
 Shin, Jae Gook 370  
 Shin, Jong 299, 345  
 Shioda, Kayoko 636, 638  
 Shipley, Mackenzie M 261  
 Shiramizu, Bruce 333  
 Shirik, Erin 322  
 Shoichet, Brian K 187  
 Shokat, Kevan M 187  
 Shoptaw, Steve 221  
 Short, Duncan 110  
 Short, William R 584  
 Shoucri, Sherif 554  
 Shuaib, Mustafa 568  
 Shweta, F N U 189  
 Shytaj, Iart Luca 313, 394  
 Siamalambwa, Quagy 477  
 Siberry, George K 646, 738  
 Sibinga, Erica 602  
 Sibiude, Jeanne 570, 582  
 Siccardi, Marco 365, 368, 374, 377, 378, 606  
 Siddiqi, Azfar-E-Alam 108, 655  
 Siedner, Mark 95, 399, 495, 497, 524  
 Siegel, Robert W 426  
 Siegler, Aaron J 636, 706  
 Sieglar, Aaron J 638  
 Sieglar, Eugenia 513  
 Sieling, Peter 272  
 Sievers, Jörg 414  
 Sigal, Alex 263  
 Sigel, Keith 166, 473, 478  
 Sigvardsen, Per Ejlstrup 499  
 Siika, Abraham 94  
 Silhol, Romain 669, 708, 733, 735  
 Siliciano, Janet 285, 293, 315  
 Siliciano, Robert 285, 293, 315  
 Silva dos Santos, Mariana 120  
 Silva, Ana 256  
 Silverberg, Michael J 97, 136, 330, 456, 468, 626, 654, 671  
 Silvestri, Guido 83, 296  
 Simoncini, Gina 752  
 Simonetti, Francesco 315  
 Simpson, Jennifer 201, 279  
 Sinclair, Gary I 127  
 Singh, Aditya 145, 745  
 Singh, Elvira 479, 485, 610  
 Singh, Kamal 382  
 Singh, Sonia 106, 687, 760  
 Singh, Vidisha 621  
 Singletery, Tyana 715  
 Singoei, Valentine 519  
 Sirajee, Reshma 592  
 Siripassorn, Krittaecho 127  
 Sirois, Patricia A 593  
 Sitdekov, Tagir 390  
 Siteo, Nadia 245, 246  
 Sivile, Suilanji 759  
 Sjöland, Carl Fredrik 658  
 Skakoon-Sparling, Shayna 776  
 Sklar, Peter 87  
 Sklutuis, Rachel 304  
 Skolasky, Richard L 337  
 Skovronsky, Daniel M 121, 122  
 Slama, Laurence 148, 537  
 Sleeman, Katrina 689  
 Sloan, Derek J 90  
 Smeaton, Laura 586  
 Smeaton, Laura M 91, 135  
 Smibert, Peter 253  
 Smieja, Marek 484  
 Smith, Alicia K 583  
 Smith, Bryan R 299, 318, 345  
 Smith, Cheryl 501  
 Smith, Colette 142, 550  
 Smith, Davey M 251, 274, 311, 396, 434, 555, 632, 692  
 Smith, Don E 417  
 Smith, James 715  
 Smith, Kimberly 402, 417, 541  
 Smith, Lauren 751  
 Smith, Melissa 305  
 Smith, Renee 593  
 Smolyarchuk, Elena 390  
 Snell, Luke 142  
 Snow, Joseph 318  
 Snyder, Chelsea 294  
 So-Armah, Kaku 99, 232, 521, 523  
 Sobieszczyk, Magdalena 554, 630  
 Sobrino, Salvador 235  
 Søgaard, Ole 310  
 Sokhela, Simiso 517, 572  
 Sokhulu, Nonhlanhla 749  
 Solanich, Xavier 256  
 Solanky, Dipesh 326  
 Solaz, Álvaro 616  
 Solomon, Isaac H 307  
 Solomon, Sunil S 135, 145, 447, 694, 719, 737, 745  
 Sommadossi, Jean-Pierre 364  
 Song, Chisu 229  
 Song, Eric 165  
 Song, Wei 702  
 Soohoo, Daniel 294  
 Sookraj, Yuktshwar 754  
 Soon-Shiong, Patrick 272, 388  
 Sophonphan, Jiratchaya 370  
 Soriano, Irene 256, 362  
 Soriano, Joan 216  
 Soriano-Arandes, Antoni 620  
 Sorrentino, Leonardo 472  
 Sortino, Ornella 237  
 Soto, Beatriz 619  
 Souares, Aurélie 633  
 Soulie, Cathia 511  
 Sousa, Ana Espada 205  
 Souza, Scott 333  
 Sovic, Brit 630  
 Sowah, Leonard 135  
 Sparén, Pär 476, 487  
 Sparrer, Konstantin 112, 213  
 Spearman, Paul 80, 196, 351  
 Speers, Suzanne 740  
 Spence, Amanda Blair 724  
 Spener-Gomes, Renata 556  
 Sperber, Hannah 234  
 Spigelman, Melvin 562  
 Spilman, Patricia R 272, 388  
 Spindler, Jonathan 639  
 Spinelli, Frank 110  
 Spinelli, Matthew 354, 355, 627  
 Spinner, Christoph 126  
 Spire, Bruno 148  
 Spivak, Adam 159  
 Spiveller, Craig A 494  
 Spreen, William R 297, 373, 401, 402, 541  
 Spudich, Serena S 163, 165, 287, 323, 340, 672, 751  
 Sreepalanjan, Somchai 340, 407  
 Srikrishnan, Aylur K 447, 719, 737  
 Srinivasula, Sharat 202, 203  
 Srithanaviboonchai, Kiengkrai 658  
 Sriudomporn, Salin 745  
 Srivastava, Meena 173  
 Ssebambulidde, Kenneth 131  
 Ssempiija, Victor 659, 725  
 Sserwadda, David 659, 725, 763  
 Ssettuba, Absalom 720  
 St Bernard, Leslie 253  
 Staadegaard, Lisa 708  
 Staggers, Kristen A 464  
 Staines, Brittany 116  
 Stalter, Randy 553  
 Stanifer, Megan 394  
 Stanley, Cole 664  
 Stannah, James 669, 708  
 Starck, Tim 633  
 Starke, Carly E 118, 201, 279  
 Stauber, Therese 492  
 Stauffer, Brian L 493, 500  
 Steeve, Boulant 394  
 Stefania, Bernardi 622  
 Stefic, Karl 698  
 Steinberg, Seth 167  
 Stella-Ascariz, Natalia 535  
 Stemer, Alexander 121  
 Stephan, Christoph 126  
 Stephens, Jeffrey 415  
 Stephens, Jessica 646  
 Stephenson, Rob 706  
 Stephenson, William 253  
 Sterling, Mara 297  
 Sterling, Timothy 726  
 Stern, Joshua 707, 710  
 Stetler-Stevenson, Maryalice 480  
 Stewart, Cameron 102, 670  
 Stewart, Eugene 422  
 Steyn, Jannetta 325  
 Steytler, John 147  
 Stillson, Christian 181  
 St-Jean, Martin 663, 664  
 Stoch, Selwyn Aubrey 88  
 Stock, Peter 467  
 Stockelman, Kelly Anne 493, 500  
 Stöckle, Marcel 457  
 Stockman, Jamila K 711, 713  
 Stoddard, Caitlin 261  
 Stokowy, Tomasz 389  
 Stone, Kimberly 478  
 Stoops, Elyssa 679  
 Stosor, Valentina 526  
 Strain, Jeremy 319  
 Strain, Matthew 288  
 Stranix-Chibanda, Lynda 177, 567, 569, 587  
 Strathdee, Steffanie 180, 632, 652

- Strickler, Howard 168  
 Stringer, Elizabeth 578  
 Stringer, Jeff 176, 578, 579  
 Stroffolini, Giacomo 335  
 Struchiner, Claudio 771  
 Strydom, Natasha 561  
 Stuckwisch, Ashley 399, 769  
 Stumpp, Michael Tobias 385  
 Stvilia, Ketevan 446  
 Styles, Tiffany M 83, 296  
 Su Lwin, Hay Mar 370  
 Su, Li-Hsin 463  
 Su, Yi-Ching 463, 465  
 Suanzes, Paula 306  
 Suárez-García, Inés 549  
 Subedi, Sony 663  
 Sucupira, Maria Cecilia A 313  
 Sudderuddin, Hanwei 283  
 Sudjaritruk, Tavitiya 614  
 Sukienik, Avery N 193  
 Sulkowski, Mark S 135, 467  
 Sullivan, Claire 501  
 Sullivan, Patrick S 636, 638, 706  
 Sun, Eugene 562  
 Sun, Hsin-Yun 132, 463, 465  
 Sun, Jing 103, 141, 536  
 Sun, Shan 590  
 Sun, Weiwei 307  
 Sun, Xiaoming 155  
 Sun, Yan 232  
 Sundararajan, Radhika 180  
 Sundermann, Erin E 327, 331  
 Sung, Kevin 261  
 Sunguti, Joram L 746  
 Sunpath, Henry 95  
 Suntarattiwong, Piyarat 595, 601  
 Supparatpinoy, Khuanchai 91  
 Suppi, Marina 207, 278, 386  
 Surial, Bernard 449, 450, 457  
 Suter-Riniker, Franziska 449, 450, 452  
 Suttichom, Duangthai 672  
 Suzuki, Kazuo 162  
 Svedhem, Veronica 487  
 Svensson, Elin 131  
 Svicher, Valentina 137  
 Swaims Kohlmeier, Alison 297  
 Swaminathan, Mahesh 143  
 Swaneveld, Francis 124  
 Swanevelde, Ronel 640  
 Swanson, Phillip A 117  
 Swanstrom, Ronald 341, 344, 384  
 Sweeney, Patricia 656  
 Swerczek, Joanna 271  
 Swindells, Susan 130, 178, 505  
 Sykes, Craig 356, 363  
 Sykes, Wendy 640  
 Symonds, Allison E 363  
 Symons, Julian A 387  
 Szabo, Brittany V 547  
 Szpiro, Adam 111
- T-**  
 Tafessu, Hiwot 663  
 Taft, Justin 388  
 Tagarro, Alfredo 596, 619, 620  
 Taha, Taha E 567, 580, 587  
 Taherzadeh, Dena 685  
 Takarinda, Kudakwashe 766  
 Takuva, Simbarashe 718  
 Talarico, Christine 401  
 Taljaard, Jantjie J 171  
 Talla, Aarthi 281  
 Tallerico, Regina 569  
 Tan, Susanna K 395  
 Tanaka, Shiho 388  
 Tang, Bin 101  
 Tang, Hsin-Yao 114, 156  
 Tang, Michael E 542  
 Tangmunkongvorakul, Arunrat 658  
 Tangnaree, Kamonkan 323  
 Tankelevich, Michael 115, 219  
 Tanner, Mary 106, 701  
 Tanser, Frank 524, 648, 649, 753  
 Tapia, Kenneth 721, 722  
 Taplin, Sarah 385  
 Tarancon-Diez, Laura 235, 597
- Tarek, Mohammad M 313  
 Tariq, Shema 727  
 Tarr, Philip 343  
 Tarrés-Freixas, Ferran 259  
 Tarumbiswa, Tapiwa 400  
 Tashima, Karen T 395  
 Tassi, Marc-Florent 698  
 Tassiopoulos, Katherine 518, 593, 667  
 Tate, Janet P 99, 454, 671  
 Tatham, Lee 379  
 Tattersall, Tessa 709  
 Tavelli, Alessandro 748  
 Tavora, Rubens 270  
 Taylor, Harry E 240  
 Taylor, James G 230  
 te Brake, Lindsey 131  
 Tedaldi, Ellen M 504, 752  
 Tegally, Houriyah 263  
 Telep, Laura H 395  
 Tellez, Francisco 445, 469  
 Tellez, María Jesús 441  
 Telwate, Sushama 191  
 Temesgen, Zelalem 380  
 Tenforde, Mark W 645  
 Tenthani, Lyson 634  
 Tepper, Vicki 602  
 Teppler, Hedy 604  
 Terrault, Norah 467  
 Teysou, Elisa 429  
 Thakkar, Jalpa 145, 745  
 Thalme, Anders 401  
 Thamburaj, Easter 145  
 Thekiso, Ntombifikele 749  
 Theodore, Deborah 554, 630  
 Thiagarajah, Shanker 505  
 Thielman, Nathan M 612  
 Thomas, Allison S 599  
 Thomas, David L 209, 447, 461  
 Thomas, Gincy 745  
 Thomas, Kanique 318  
 Thomas, Katherine K 553  
 Thomas, Réjean 651  
 Thomas, Reuben 310  
 Thompson, Tezha 218  
 Thomsen, Magda Teresa 402  
 Thomsen, Nathan 425  
 Thorball, Christian A 224  
 Thorne, Claire 586  
 Thorne, Julie 743  
 Thornhill, John 142  
 Thrift, Aaron P 471  
 Thrun, Mark 397  
 Thudium, Rebekka Faber 499, 532  
 Thulare, Hilary 563, 564, 769  
 Thurman, Michelle 382  
 Tiam, Appolinaire 182  
 Tian, Yuan H 395  
 Tien, Phyllis 510, 526, 538  
 Tinago, Willard 96, 100, 231, 258, 491  
 Tindle, Hilary A 99  
 Tinevez, Jean-Yves 78  
 Tingler, Ryan 716  
 Tipsuk, Somporn 340, 672  
 Tiraboschi, Juan M 256, 358, 362, 413  
 Tirschwell, David 98  
 Titanji, Boghuma K 232  
 Tlali, Mpho 662  
 Tobery, Amanda 203  
 Tobian, Aaron 681  
 Tobian, Frank 633  
 Tobin, Nicole 221, 604  
 Tocha, Christopher 686  
 Todd, John-Paul 82  
 Tokuyama, Minami 115, 211, 219  
 Tolba, Mahmoud M 394  
 Tolstrup, Martin 310  
 Tomai, Mark 618  
 Tomov, Dimitre 317  
 Tompkins, Lauren 204  
 Toner, Mehmet 352, 353  
 Torán-Monserrat, Pere 210, 264  
 Torben, Workineh 84  
 Torbett, Bruce E 434  
 Tordoff, Diana M 138  
 Torian, Lucia 107
- Tornheim, Jeffrey A 209  
 Torrella, Ariadna 306  
 Torres, Ferran 412  
 Toska, Elona 589  
 Tostão Neiva, Maria Ines 205  
 Totonchy, Jennifer 169  
 Touizer, Emma 262  
 Towler, Andrea 474  
 Towner, William J 330  
 Townes, Ashley R 701  
 Townley, Ellen 604  
 Toy, Junine 628  
 Tracy, Russell 521, 523  
 Trahey, Meg 257  
 Tran, Vilinh 512  
 Trautmann, Lydie 154, 280, 595, 672  
 Travassos, Paula 556  
 Trebicka, Jonel 455  
 Tremblay, Cécile 651  
 Treuth, John William 493  
 Triant, Virginia A 495  
 Tribut, Heather J 548  
 Trigg, Jason 664, 709  
 Trinité, Benjamin 259  
 Tribout, Heather J 548  
 Trigg, Jason 664, 709  
 Trinité, Benjamin 259  
 Tribout, Heather J 548  
 Trocha, Alicja Piechocka 283  
 Trombetta, Amelia Chiara 205  
 Trøseid, Marius 532  
 Trotta, Diane 483  
 Troya, Jesús 339, 641  
 Trofio, Mattia 335  
 Truong, Hoa 294  
 Tsai, Olivia 283  
 Tse, Victor 384  
 Tseng, Alice 372  
 Tseng, Chi-Hong 181  
 Tsikhutsu, Isaac 519  
 Tsuei, Torie 163  
 Tsui, Judith I 683  
 Tsybovsky, Yaroslav 86  
 Tuazon, Jasmine 383  
 Tubiana, Roland 570  
 Tugume, Lillian 131  
 Tuhebwe, Doreen 720  
 Tukei, Betty 182  
 Tukei, Vincent 182  
 Tukuru, Sade 630  
 Tung, Audrey Gemma 664  
 Turcotte, Isabelle 298  
 Turkova, Anna 174  
 Turner, Emilee H 333  
 Turner, Katherine M E 708  
 Turner, Megan 726  
 Tu-Sekine, Becky 515  
 Tuttle, Jay L 121  
 Twizere, Christelle 614  
 Tzou, Philip L 423
- U-**  
 Uberti-Foppa, Caterina 611  
 Ubolyam, Sasiwimol 179, 370  
 Ueaphongsukkit, Thornthun 370  
 Uffmann, Emilie A 296  
 Ukaere, Amalachukwu 736, 774  
 Uldrick, Thomas S 167, 474, 480  
 Umlauf, Anya 331  
 Underwood, Mark 414  
 Unger, Jennifer A 566, 577  
 Upadhyay, Amit 118  
 Upadhyay, Chitra 250  
 Upadhyay, Ojesh 505  
 Urbaitye, Rimgaile 414  
 Uribe, Claudia 260  
 Uriu, Keiya 113  
 Urrea, Victor 226, 259, 300  
 Ustianowski, Andrew 508  
 Utay, Netanya Sandler 212, 222  
 Utz, Gregory 318
- V-**  
 Vaccari, Linda Cheyenne 684  
 Vaddady, Pavan 376  
 Vaia, Francesco 545  
 Vaida, Florin 317, 331  
 Vaillancourt, Peter 426  
 Valcarce, Nieves 227
- Valcour, Victor 163, 323, 340  
 Valdez, Rogelio 252  
 Valencia, Eulalia 453, 460, 534  
 Valentine-Graves, Mariah 636, 638  
 Valenzuela-Fernández, Agustín 226  
 Van Bakel, Harm 211  
 Valenzuela-Ponce, Humberto 251  
 Van Beek, Jan E A 695  
 Van Bremen, Kathrin 455  
 Van den Berg, Karin 640  
 Van den Heuvel, Leigh 662  
 Van der Merwe, L Leigh Ann 657  
 Van der Merwe, Tian 171  
 Van der Straten, Ariane 147, 728  
 Van Deventer, Anneen 680  
 Van Dijk, Janneke 615  
 Van Dijk, David 287  
 Van Duyn, Rachel 424  
 Van Ert, Hanora 389  
 Van Eygen, Veerle 297, 402, 541  
 Van Gils, Marit J 120  
 Van Heerden, Alastair 111, 755  
 Van Horne, Brian 204  
 Van Kampen, Jeroen J A 124, 695  
 Van Kuppeveld, Frank J M 385  
 Van Lettow, Monique 585, 615  
 Van Nguyen, Kinh 565  
 Van Niekerk, Magriet 171  
 Van Oosterhout, Joep J 181, 585  
 Van Rompay, Koen KA 270, 618  
 Van Rooyen, Heidi 111, 755  
 Van Solingen-Ristea, Rodica 402, 403, 505, 541  
 Van Wyk, Jean Andre 414, 417, 489, 505  
 Van Zyl, Gert 594  
 Van, Tran A 436  
 Vance, David 324  
 Vance, Patricia 347  
 Vandamme, Niels 215  
 Vandekerckhove, Linos 215  
 Vanderford, Thomas H 118, 157  
 Vandermeulen, Kati 401  
 VanderVeen, Laurie 128  
 Vandormael, Alain 648  
 Vandyck, Koen 387  
 Vannappagari, Vani 505, 584  
 Vanobberghen, Fiona 431  
 Vanveggel, Simon 402  
 Varabyou, Ales 305  
 Vargas, Montserrat 194  
 Varghese, Elizabeth 260  
 Vargo, Ryan 87, 88, 376  
 Varriale, Joseph 293  
 Varshney, Karan 631  
 Vasan, Sandhya 154, 163, 179, 323, 340, 359, 407, 408, 672  
 Vásquez, Elizabeth 538  
 Vassilenko, Anna 443  
 Vauloup-Fellous, Christelle 582  
 Vaz, Paula 245, 246  
 Vázquez Alejo, Elena 597  
 Veazey, Ronald S 277  
 Vecchio, Alyssa 321, 341  
 Veenhuis, Rebecca 322  
 Vega, Teresita 481  
 Veloso, Sergi 194  
 Veloso, Valdilea 771  
 Velu, Vijayakumar 583  
 Vendrame, Elena 220  
 Venneri, Mary Anna 208, 470  
 Venter, Francois 517, 572  
 Ventura, John D 285  
 Vera-Méndez, Francisco J 469  
 Veras, Nazle 741  
 Verbon, Annelies 695  
 Verdier, Rose-Irene 185  
 Vergara, Candelaria 459  
 Vergori, Alessandra 242, 334, 336, 545  
 Verheij, Eveline 237  
 Verma, Mohit 272  
 Vermeulen, Marion 640  
 Vernon, Andrew 130  
 Vestbo, Jørgen 532  
 Vhembo, Tichaona 569  
 Viala, Benjamin 343  
 Vicenti, Ilaria 693

- Vickerman, Peter 440, 708, 733  
 Vidal, Francesc 194, 549  
 Vidal, Samuel J 717  
 Vigil Vázquez, Sara 616  
 Vigil-Vazquez, Sara 581  
 Vignuzzi, Marco 187  
 Vigón, Lorena 159  
 Viladés, Consuelo 194  
 Vilgelm, Anna 214  
 Villanueva, Mercedes 740  
 Villaverde, Serena 619, 620  
 Vinikoor, Michael J 615  
 Vinton, Carol 201, 279  
 Violán-Fors, Concepción 210, 264  
 Violari, Avy 587, 604, 605  
 Viox, Elise 118  
 Virga, James Q 222  
 Viscido, Agnese 266  
 Visconti, Adam J 643, 724  
 Vishwanathan, Sundaram Ajay 146  
 Vitale, Mirriah 186  
 Vivancos, María Jesús 413, 441  
 Vivanti, Alexandre J 582  
 Vivar Ramon, Christian 332  
 Vojnov, Lara 568  
 Volberding, Paul 276  
 Volcic, Meta 112  
 Volpe, Karen E 325  
 Vrancken, Bram 632  
 Vreeman, Rachel C 614  
 Vriesde, Marion E 695  
 Vujkovic-Cvijin, Ivan 237  
 Wwalika, Bellington 578, 579
- W-**  
 Wa Katolo, Henriette 742  
 Wadonda, Nellie 634  
 Wagner, Anjuli D 674, 707  
 Wagner, Gabriel 705  
 Wagner, Martin 213  
 Wagner, Philippe 476, 487  
 Wagner-Cardoso, Sandra 135  
 Waitt, Catriona 175  
 Waja, Ziyaad 130  
 Wald, Anna 721, 722  
 Walensky, Rochelle P 150, 670  
 Walimbwa, Stephen Ian 94, 368  
 Walker, Bruce D 225, 283  
 Wallin, Jeffrey 220  
 Wallis, Carole 563, 564  
 Wallner, Jackson J 239  
 Walmsley, Sharon 448  
 Walser, Marcel 385  
 Walsh, Hannah 751  
 Walunas, Theresa L 393  
 Wamalwa, Dalton 558  
 Wan, Hong 604  
 Wandeler, Gilles 449, 450, 452, 457, 565  
 Wang, Cheng 446  
 Wang, Chuangqi 274  
 Wang, Cuiwei 168  
 Wang, Duolao 175  
 Wang, Guohong 354  
 Wang, Han 114  
 Wang, Hao-Wei 480  
 Wang, Jiuzhou 492  
 Wang, Kelly 717  
 Wang, Lu 776  
 Wang, Mei Cheng 209  
 Wang, Melody 721, 722  
 Wang, Ruolan 417  
 Wang, Shiyi 434  
 Wang, Songping 197, 198, 230  
 Wang, Su 393  
 Wang, Xiao Qian 314  
 Wang, Xinxin 430  
 Wang, Xueyuan 105  
 Wang, Xun 483  
 Wang, Yuanyuan 401, 402, 541  
 Wang, Zeyuan 232  
 Wang, Zichen 302  
 Wanjalla, Celestine 522, 523, 531  
 Wara, Nafisa J 769  
 Ward, Douglas 504  
 Warszawski, Josiane 570  
 Wasmuth, Jan-Christian 455
- Waters, Laura 262  
 Watkins, Meagan 277  
 Watoyi, Salphine 707, 710  
 Watson, Dovie L 723  
 Wattananimitgul, Nattanicha 150  
 Watts, Brian 268  
 Wawer, Maria 321, 341, 720  
 Weaver, Nicholas 80  
 Webb, Emily 133  
 Webb, Lindsey 602  
 Webb, Sharon 586  
 Weber, Allison R 543  
 Weber, Kathleen 288, 538, 539  
 Wei, Stanley C 660  
 Weil, Tatjana 213  
 Weinreich, David M 123  
 Weiss, Julian 751  
 Weiss, Kevin 473  
 Weissler, Vanessa L 88  
 Weissmann, Simon 482  
 Weitzmann, M Neale 230  
 Wejnert, Cyprian 712  
 Welker, Andreas 633  
 Welker, Jorden L 408  
 Wellons, Melissa 523  
 Welte, Alex 640  
 Wendell, Debbie 105  
 Weragalaarachchi, Krishanthi 214  
 Wertheim, Joel 251, 653  
 Wesolowski, Amy 694  
 West, Steve 89, 375  
 Westmoreland, Drew A 637  
 Whelan, Sean P J 188  
 Whitaker, Jennifer 464  
 Whitby, Denise 167, 480  
 White, Brittany 289, 461  
 White, Donna L 471  
 White, Jennifer A 315  
 White, Kirsten L 430, 438  
 White, Kris M 187  
 White, Nicole 356, 357, 363  
 Whiteside, Lauren 683  
 Whitney, Bridget M 409, 468, 543  
 Wiche Salinas, Tomas Raul 233  
 Widdowson, Andrew 684  
 Widell, Anaida 167, 480  
 Wiebold, Amanda 299  
 Wiegand, Ann 304, 424  
 Wiener, Jeffrey 696  
 Wiesner, Lubbe 371  
 Wijewantha, Yasasvi 214  
 Wilcox, Ronald 533  
 Wilhelm, Kay 552  
 Williams, Andrew 97  
 Williams, Brianna 204  
 Williams, Christopher G 645  
 Williams, Deborah 540  
 Williams, Dionna 321, 322  
 Williams, Nick 475  
 Williams, Paige L 571, 573, 611  
 Williamson, Marie 142  
 Willig, Amanda 102, 510  
 Wills, Genevieve 562  
 Wilson, Cara 218  
 Wilson, Ethan A 580, 678, 680, 682  
 Wilson, Jimmy 119  
 Wilson, John W 380  
 Wilson, Michael 165  
 Wilson, Tracey 539  
 Wimbish, Chanelle 135  
 Winchester, Lee 368  
 Wingood, Gina 539  
 Winston, Alan 540  
 Wirtz, Andrea 657  
 Wit, Ferdinand W 237  
 Witt, Daniel 773  
 Wiznia, Andrew A 605  
 Woelk, Godfrey 746  
 Wohl, David A 396, 410, 411, 415, 555  
 Wojna, Valerie 333, 350  
 Woldemeskel, Bezawit Abi 223  
 Woldesenbet, Selamawit A 757  
 Wolf, Caitlin R 261  
 Wolinsky, Steven 324  
 Wong, Alison YJ 372
- Wong, Cherise 102  
 Wong, Chun-Shu 243  
 Wong, Colline 276  
 Wong, Emily B 524  
 Wong, Joseph K 191  
 Wong, Michelle E 291  
 Wong, Raymond 272  
 Wood, Cheyret 218  
 Wood, Sarah M 723  
 Woods, Christopher 116  
 Woodworth, Brendon 248  
 Woolley, Elizabeth 91  
 Wools-Kaloustian, Kara 109, 509, 743  
 Workowski, Kimberly 415  
 Wright, Jessica A 380  
 Wright, Jonathan 417  
 Wu, Baohua 108  
 Wu, Fengting 293  
 Wu, George 393  
 Wu, Guoxin 316  
 Wu, Kuan-Sheng 705  
 Wu, Margaret 481  
 Wu, Sterling 402, 505, 541  
 Wu, Yingfeng 761  
 Wu, Yumeng 630  
 Wyen, Christoph 159  
 Wyka, Katarzyna 109  
 Wyke, Sally 753  
 Wyles, David 135  
 Wynne, Brian 414, 417, 489
- X-**  
 Xaba, Gugu 749  
 Xia, Fan 553  
 Xing, Enming 383  
 Xu, Ke 232, 521  
 Xu, Min 129  
 Xu, Shihao 244  
 Xu, Yanxun 321
- Y-**  
 Yacoub, Anne D 337  
 Yager, Jenna Lynn 366, 367  
 Yagnik, Bhruvu 83, 157  
 Yakubova, Elena 390  
 Yamshchikov, Galina V 160  
 Yan, Joyce 769  
 Yancopoulos, George D 123  
 Yang, Isabelle T 495  
 Yang, Jasper 642  
 Yang, Jincheng 608  
 Yang, Jingyan 518  
 Yang, Jun 195  
 Yang, Weiming 250  
 Yant, Stephen 717  
 Yapa, Handurugamage Manisha 753  
 Yaphe, Sean 629  
 Yarbrough, Wendell G 481  
 Yarchoan, Robert 167, 170, 475, 480  
 Yared, Nicholas 629  
 Yates, Adam 408  
 Yazdani, Kiana 628  
 Yazdanpanah, Yazdan 416, 419  
 Ye, Fei 531  
 Ye, Monica 664  
 Yee, Kelly 604  
 Yee, Lynn M 573, 575  
 Yee, Randy 143  
 Yeh, Eunice 396  
 Yeh, Yang-Hui 305  
 Yendewa, George A 410, 411, 548  
 Yende-Zuma, Nonhlanhla 567  
 Yeregui, Elena 194  
 Yeung, Stephen 528  
 Yiannoutsos, Constantin 509, 614  
 Yilmaz, Aylin 487  
 Yin, Michael T 212, 332, 554  
 Yin, Xiangfan 114, 156  
 Ying, Roger 755  
 Yingst, Samuel 679  
 York, Vanessa 98, 254  
 Yost, Fredrick 238  
 You, William X 637  
 Young, James 456  
 Young, Katherine 134  
 Yount, Jacob 383
- Yu, Danyang 321  
 Yu, Helen 294  
 Yu, Lei 703  
 Yu, Qigui 591  
 Yu, Tong 209  
 Yu, Wendy 611, 613  
 Yu, Wen-Han 274  
 Yu, Xu 155, 225, 307, 309, 437, 598  
 Yuen, Courtney M 560  
 Yuengling, Katherine 634  
 Yuki, Steven A 191  
 Yun, Cassandra A 627
- Z-**  
 Zabih, Sara 221  
 Zacharopoulou, Penny 158  
 Zago, Daniela 693  
 Zahn, Ryan J 706  
 Zambia, Kevin M 600  
 Zamecnik, Colin 165  
 Zanchetta, Marisa 623  
 Zandi, Peter 102  
 Zang, Xiaowei 87, 88  
 Zangeneh, Sahar Z 580  
 Zaniewski, Elizabeth 614  
 Zanni, Markella V 494, 496, 498, 506  
 Zash, Rebecca 176, 571, 575, 576, 588  
 Zauanders, John 162  
 Zazzi, Maurizio 693  
 Zeh, Clement 435, 689  
 Zelazny, Adrian 243  
 Zemanek, Jillian 716  
 Zera, Chloe 571  
 Zerbato, Jennifer 301  
 Zeuli, John D 380  
 Zhan, Joyce 126  
 Zhang, Kudon, Hui 702  
 Zhang, Chunyang 377  
 Zhang, Guoqing 689  
 Zhang, Hao 293  
 Zhang, Hui 250  
 Zhang, Liao 220  
 Zhang, Peng 86, 271  
 Zhang, Shaoyi 630  
 Zhang, Wendy 709  
 Zhang, Xu 369  
 Zhang, Yuexiu 383  
 Zhang, Yuwei 233  
 Zhao, Chunxia 146  
 Zhao, Gagarin 107  
 Zhao, Theodore 111  
 Zheng, Jia-Hua 92  
 Zheng, Jim 717  
 Zheng, Wenshu 558  
 Zhou, Shuntai 384  
 Zhou, Siyanai 589  
 Zhou, Xiao-Jian 364  
 Zhu, Weiming 106, 696, 701, 703, 731, 739  
 Zhu, Yuan-Shan 513  
 Zhyvoloup, Alexander 233  
 Zidar, David A 497  
 Ziegler, Thomas R 512  
 Zielinski, Lindsay 765  
 Ziema, Lauren 176, 177  
 Zilberstein, Netanel F 114  
 Zimba, Rebecca 637  
 Zimba, Suzgo 746  
 Zimmermann, Liv 394  
 Zions, Danielle 769  
 Zipparo, Mary E 255  
 Zitt, Christof 385  
 Zlot, Amy 144  
 Zolla-Pazner, Susan 250  
 Zolopa, Andrew 110  
 Zuck, Paul 316  
 Zucker, Jason 554, 630  
 Zuma, Thembelihle 753  
 Zyambo, Khozva D 759