16th Annual
Duke Center for AIDS Research
Virtual Fall Scientific Retreat

September 29, 2020
9am-2pm

ZOOM LINK to retreat

Virtual Poster Sessions run from 12:30—2:00
A very hearty welcome to the 16th annual CFAR Fall Scientific Retreat, this being our first virtual Retreat, necessitated by the ongoing COVID 19 pandemic. I truly hope that this greeting finds each of you safe, healthy, and diligently practicing ‘social distancing’. Just as last year was dominated by our efforts focused on writing our CFAR competitive renewal, this year has brought us all a whole new set of unanticipated challenges in trying to negotiate the pandemic while still remaining productive in our ongoing research activities. So, let me begin by sharing the tremendously good news that our CFAR competitive renewal application was well-received by the NIH-IRG, and we were awarded full funding for the next 5 years. As we mentioned during the last Retreat, we now have maintained an NIH AIDS-related Funded Research Base (FRB) in excess of $40 million over the last 2 years, thus qualifying us to move from a Tier 1 to a Tier 2 CFAR, which brings with it an increase in total annual CFAR funding from $1.5 million to $2.25 million for each of the next 5 years. In addition to many possible new initiatives, the increased funding will permit us to further expand CFAR support services within our Cores as well as provide additional funds for enhanced community outreach and engagement activities.

For the past 15 years, this Fall Scientific Retreat has served as the focal point of the annual CFAR support activities. Perhaps its most popular aspect was the poster session that served as an important networking event. Now that we need to move to a virtual format, it will be difficult to fully capture this important sense of community. Admittedly, what we are doing today is conducting a grand experiment into the many aspects of a virtual Retreat using a Zoom format. We are fortunate to have received sage guidance from Joanna Downer, the Associate Dean for Research Development at Duke, who has broad experience in this arena. Our greatest overall concern is that the Early Stage Investigators, especially those with poster presentations, get the important feedback concerning their ongoing research projects that they would otherwise get with a face-to-face meeting during a ‘normal’ CFAR Retreat. According to our plan, each ‘Poster’ presenter will have their own individual Zoom room that Retreat attendees can visit during an allocated 90-minute time slot. Rather than a poster, we’ve requested that each presenter compose 3-5 slides that provide the requisite details normally found on a poster. We have over 20 ‘poster’ presentations, which means over 20 individual Zoom rooms that can be visited by the Retreat participants. Instructions on how to log into each room can be found among the provided program materials for the Retreat. With the exception of the poster presentation format, the rest of the Retreat will proceed much like a normal Zoom meeting that has now become so familiar to us all.

We truly hope that our ‘excellent adventure’ will proceed without a hitch, but ask your kind indulgence and patience if technical problems do arise. We would value any constructive comments and suggestions that you might have after the Retreat concludes. Finally, sincerest thanks for your continued participation in Duke CFAR events throughout the year. Please remember that the Duke CFAR exists in order to provide each of you with critical infrastructure support as you conduct your important HIV/AIDS-related research activities aimed at impacting the ongoing HIV epidemic.

Kent J. Weinhold, PhD
Director
Duke CFAR
Sixteenth Annual CFAR Fall Scientific Retreat
Virtual Meeting
September 29, 2020

9:00 – 9:15 AM  Welcome, Updates on the Duke CFAR, and Plans for Year 16
Kent J. Weinhold, PhD, Duke CFAR Director

9:15 – 9:20 AM  T32 Outstanding Leadership in Scientific Mentoring Award
Georgia D. Tomaras, PhD, Nathan M. Thielman, MD, and Guido Ferrari, MD
Co-Directors, Interdisciplinary Research Training Program in AIDS

CFAR Core Updates
Moderator: Kent J. Weinhold

9:20 – 9:25 AM  Developmental Core
Herman F. Staats, PhD, Director, CFAR Developmental Core

9:25 – 9:30 AM  Immunology Core
Georgia D. Tomaras, PhD, Director, CFAR Immunology Core

9:30 – 9:35 AM  Quantitative Sciences Core
Cliburn Chan, PhD, Co-Director, CFAR Quantitative Sciences Core

9:35 – 9:40 AM  Clinical Core
Coleen K. Cunningham MD, Co-Director, CFAR Clinical Core

9:40 - 9:45 AM  Social and Behavioral Sciences Core
Amy L. Corneli, PhD, MPH, Director, CFAR SBS Core

9:45 - 9:50 AM  Biomedical Preventions Scientific Working Core
Mehri S. McKellar, MD, Co-Director, CFAR SWG

Oral Presentations from Selected Abstract Submissions
Moderator: Susanna Naggie

9:50 - 10:05 AM  Hira Anees Awan
‘Investigating the impact of preexisting CMV immunity on the risk of HIV acquisition in HVTN505 vaccine efficacy trial for HIV’

10:05 - 10:20 AM  Emilie Uffman
‘Kinetics of Vaccine-Elicited Antibodies in HIV-exposed infants from Botswana’

10:20 - 10:35 AM  Brandon Knettel, PhD
‘The Roles and Effectiveness of Community Health Workers in Supporting HIV Care Engagement and Well-Being Among Adults Living with HIV in Kilimanjaro, Tanzania’

10:35 – 10:40 AM Wrap-up/Discussion

10:40 – 11:00 AM  BREAK

CFAR Scientific Presentations
Moderator: Georgia Tomaras

11:00 - 11:20 AM  Michael V. Relf, PhD
Associate Director, Social & Behavioral Science Core, CFAR Faculty, Current Pilot Grant Recipient
‘Contextualizing a Stigma Reduction Intervention to be Linguistically and Culturally Relevant for Women Living with HIV in Rwanda and Tanzania’

11:20 - 11:40 AM  Kathryn Whetten, PhD & Sara H. LeGrand, PhD
CFAR Faculty Members, Previous Pilot Grant Recipients
Sexual and Gender Minority Health Program

11:40 - 12:00 PM  Kevin Tsai, PhD
CFAR Member, 2019 Pilot Grant recipient
‘Acetylation of Cytidine Residues Boosts HIV-1 Gene Expression by Increasing Viral RNA Stability’

12:00 - 12:30 AM  AMP Trial: Duke Data and Way Forward
David C. Montefiori, PhD, ‘nAb Titer and Virus Sensitivity’
Kelly E. Seaton, PhD, ‘PK Measurements’
Coleen K. Cunningham, MD, ‘Broadly Neutralizing Antibodies to Prevent Vertical Transmission of HIV’

Poster Session

12:30 – 2:00 PM  Poster Presentations
Links to Zoom Poster Presentations are located in the Retreat Program
CFAR DEVELOPMENTAL CORE UPDATES

NEW AWARDS FOR YEAR 15/16

CFAR Pilot Awards

*Examining the Impact of Marijuana Metabolites on Immune and Cognitive Function*
Sheri Towe, PhD

*Metabolomic Profile in Risk Prediction of Fibrosis Among People with HBV and HIV Coinfection*
Tzu-Hao “Howard” Lee, MD

*Tackling a Neglected HIV-Associated Infection - A Validation Study of the IgG and IgM Serological Responses to Talaromycosis*
Shanti Narayanasamy, MD

CFAR Supplement Awards

National Institute of Health- EtHE Team-initiated Implementation Research

*PrEP-MECK: Increasing PrEP uptake among Same Gender Loving Men in Mecklenburg County, North Carolina*
Amy Corneli, PhD
CFAR Microgrants

*Advancing PrEP Delivery: An Assessment of the Readiness of Key Stakeholders for the Delivery of PrEP in the Urgent Care Setting*

Charles Burns, MD

*Contextualizing Factors Associated with Non-Adherence to Cardiovascular Disease Prevention Strategies for People Living with HIV Who Have Achieved Viral Suppression*

Charles Muiruri, PhD

CFAR FACULTY SUPPORT

CFAR Year 15/16 Faculty Awards

*Hrishikesh Chakraborty, DRPH*
Associate Director
Duke Clinical Research Institute

*Brandon Knettel, PhD*
Assistant Professor
School of Nursing
NEW OUTCOMES FROM CFAR AWARDS

NIH Grants awarded 2020

Joy Noel Baumgartner, PhD
R01 Award      NICHD  2020 – 2025
Adolescent Wellness Visits to Reduce Health Risks

Tiarney Ritchwood, PhD
K08 Award      NIMH  2019 - 2024
Social support to retain adolescents living with HIV in care and improve ART adherence

CFAR Linked Publications


Oral Presentations
Oral presentations are chosen from submitted abstracts. Congratulations to Hira Anees Awan, Emilie Uffman, and Brandon Knettel!

Title: Investigating the impact of preexisting CMV immunity on the risk of HIV acquisition in HVTN505 vaccine efficacy trial for HIV

Hira Anees Awan is a Fulbright scholar from Pakistan, currently pursuing her master's degree in Biostatistics at Duke University. Her research interests include statistical data analysis, predictive modeling, and computational immunology. She plans to pursue a Ph.D. degree in Biostatistics and work on applying deep learning algorithms on immunological data. Hira is a participant in the 2020 Duke Quantitative Summer Internships for HIV/AIDS Research for graduate students in a quantitative discipline.

Title: Kinetics of Vaccine-Elicited Antibodies in HIV-exposed infants from Botswana

Emilie Uffman, graduated with a Bachelor's of Science in Biology from Davidson College in May 2019. She works as a Research Technician in the laboratory of Giny Fouda at DHVI. Emilie's work focuses on investigating the antibody kinetics of HIV-infected plasma samples by ELISA and BAMA assays. She is also a part of the protein production team. Emilie plans to attend medical school and serve women and children in her career.

Title: The roles and effectiveness of community health workers in supporting HIV care engagement and well-being among adults living with HIV in Kilimanjaro, Tanzania

Brandon Knettel, Ph.D. is a licensed psychologist and newly appointed assistant professor in the Duke University School of Nursing with a secondary appointment in the Duke Global Health Institute. His areas of specialization are global mental health and health behavior, with a focus on care engagement, stigma reduction, and mental health support for people living with HIV. Dr. Knettel's international projects are primarily located in Moshi, Tanzania, where he recently completed a one-year VECD Fogarty Global Health Fellowship to evaluate a community health worker program for HIV care engagement. Dr. Knettel has been a member of the Duke CFAR since 2016 and previously served as Coordinator of the Social and Behavioral Sciences Core.
Research Category: Basic/Translational

Hira Anees Awan  
hiraanees.awan@duke.edu  
Graduate student at Duke University  
Biostatistics and Bioinformatics  
César L. Angel, Janice McCarthy, Georgia Tomaras

**Title:** Preexisting CMV immunity is associated with blunted vaccine specific cellular and humoral responses and increased risk of HIV acquisition in phase IIb human vaccine efficacy trial

**Introduction:** Despite decades of testing, an effective HIV-1 vaccination strategy has not been established. However, immunological data from limited efficacy HIV-1 vaccine trials have revealed correlates of risk and highlighted possible protective mechanisms using a systems vaccinology approach. On the other hand, several studies have demonstrated a robust imprinting on the human immune system by cytomegalovirus (CMV), with conflicting reports on the role of preexisting CMV immunity on shaping heterologous vaccination responses.

**Objectives:** The primary purpose of this study was to investigate the role of preexisting CMV immunity on the risk of HIV acquisition in phase IIb HIV-1 vaccine efficacy trial - HIV Vaccine Trials Network 505 (HVTN505). In addition, we independently explored the correlation of all immunological parameters with the risk of HIV acquisition and preexisting CMV immunity.

**Methods:** In this study, we integrated various measurements of HIV- and CMV-specific humoral and cellular responses, antibody functionality, along with baseline and post-vaccination systemic cytokine measurements from cases (N = 44) and controls (N = 145) of the HVTN505 trial. Towards identifying the immunological parameters associated with CMV, we performed univariate and multivariable analyses. For univariate analysis, Mann Whitney U-test was performed for each parameter, whereas for multivariable analysis, a multiple linear regression model was developed for each variable. In each of multiple linear regression model, the response variable was the immunological parameter being explained by different predictors including age, behavioral risk, race, and treatment. Multiple hypotheses testing problem was addressed using the Benjamini-Hochberg method. A similar set of analyses were performed for the risk of HIV acquisition. The only difference was that for multivariable analyses, we included CMV status as an additional predictor. For further analyzing the effect of preexisting CMV immunity on risk, we restricted our pool of variables to the ones that have either been previously linked to the risk of HIV acquisition or have never been investigated from HIV acquisition risk point of view. This reduced feature set was used to build the LASSO logistic regression model to further select the variables that are significantly associated with the risk of HIV acquisition. 10-fold cross validation was used to determine the value of the tuning parameter.

**Results & Conclusion:** Employing this systems vaccinology approach, we found that preexisting CMV immunity is associated with a baseline elevation of systemic pro-inflammatory cytokines, depressed mitogenic and chemoattractant cytokine responses, diminished HIV-specific cellular and humoral immunity and antibody functionality, and with increased risk of HIV-1 acquisition. We also identified an association between increased HIV-1 acquisition and higher baseline levels of interferon (IFN)γ and IFNγ-induced protein 10. Overall, our findings suggest a role of prior CMV infection in dampening vaccination responses, and of the IFNγ pathway in HIV-1 acquisition in the setting of vaccination. These results offer baseline parameters that might predict outcome and can inform the design of future HIV-1 vaccine trials.
Kinetics of Vaccine-Elicited antibodies in HIV-exposed infants from Botswana
Uffman, Emilie, Shuk Hang (Grace) Li; Ganga Moorthy, MD; Rebecca R. Young, MS; Genevieve Fouda, MD, PhD; Matthew S. Kelly, MD, MPH

**Background:** Respiratory infections, such as respiratory syncytial virus (RSV) and pneumococcal pneumonia, remain the leading causes of lower respiratory tract infections and mortality among children globally. HIV-exposed, uninfected infants are particularly susceptible to respiratory infections and have higher early childhood mortality than HIV-unexposed infants. Factors that could contribute to this increased susceptibility of HIV-exposed uninfected children include feeding practices, maternal illness, and suboptimal immune responses to vaccination. In this study, we aim to determine the effect of HIV exposure on the immunogenicity of a pediatric vaccine panel in a cohort of infants in Botswana.

**Methods:** We obtained plasma samples from 74 children from Botswana at 0, 5, and 12 months of age. We measured their antibody responses against the 13 serotypes of *S. pneumoniae* (PnP) contained within 13-valent pneumococcal conjugate vaccine using an enzyme-linked immunoabsorbent assay (ELISA). A pediatric vaccine multiplex assay (PVMA) was used to detect antibody binding to a panel of bead-conjugated pathogens. Median fluorescent intensity (MFI) of the samples was measured. Bio-Plex Manager was used to interpolate concentrations from standard curves.

**Results:** The magnitude of the antibodies increased following vaccination and was higher at 5 months than at birth for all 13 serotypes of PnP, diphtheria, pertussis, and *Haemophilus influenzae* type B. However, antibody levels rapidly decreased and the levels at 12 months of age were significantly lower than at 5 months. Infants were born with antibodies against hepatitis B, tetanus, rubella, and RSV, however the antibody levels declined significantly from birth to 5 months of age. At 12 months of age, most infants had continued low antibody levels. However, some infants had an increase in antibody levels from 5 months of age, indicative of infection.

**Conclusions:** Our results indicate that infants from Botswana develop robust antibody responses following vaccination, but these antibodies wane rapidly during infancy. The clinical significance of this rapid decline is unclear. Vaccine strategies capable of inducing robust, durable antibody responses or an additional vaccine booster may be required to ensure protection from respiratory infections throughout childhood.
Research Category: Social/Behavioral

Full Name: Brandon Knettel
email address: brandon.knettel@duke.edu
Job Title: Assistant Research Professor
Departmental Affiliation: School of Nursing, DGHI
Mentor (if applicable): Michael Relf, Ph.D.

**Background:** In low-resource settings, community health workers (CHWs) have been successfully trained to offer many HIV services, including testing, counseling and mental health support. In Tanzania, the central government oversees a national cohort of volunteer CHWs to support HIV care engagement, known as Community-Based HIV Services (CBHS). The goals of this study were to evaluate the CBHS program by: (1) obtaining stakeholder feedback on strengths and limitations of the program, and (2) determining whether contact with CHWs facilitated engagement in HIV care and patient well-being.

**Methods:** We conducted semi-structured qualitative interviews with 4 CBHS program administrators, 8 clinic nurses, 18 CHWs, and 18 patients living with HIV at two urban clinics in Moshi, Tanzania. We then enrolled a prospective cohort of 80 patients initiating HIV care to complete baseline and 3-month follow-up measures of demographics, HIV history, well-being, and care engagement. We analyzed the qualitative interview data through a team-based, inductive approach. For the cohort data, we performed a descriptive analysis and used logistic regression and correlation coefficients to make inferences concerning the data.

**Results:** Qualitative interviews across participant groups emphasized the value of CHWs in care engagement, but also lapses in communication and lack of clarity about the responsibilities of CHWs. Nurses felt they had little time to track patients with care engagement challenges and appreciated CHW assistance in this area. Patients were intended to have an introductory meeting with a CHW; however, only 58% of patients were informed of the program at care initiation and only 22 (28%) had an introductory meeting. The CHWs described the work as personally fulfilling but emotionally taxing and felt the small stipend they received for transportation was not enough to adequately support the work. In the cohort study, patients under 35 years of age (OR=3.4; 95% CI 1.8-5.6, p=0.003) and those who screened positive for depression (OR=9.3, 95% CI 1.4-18.6, p=0.018) had significantly higher odds of experiencing care engagement challenges. Notably, contact with a CHW did not significantly impact HIV care engagement and was not associated with improvements in depressive symptoms, stigma, or attitudes about medication. Unfortunately, the observed power of the study to detect impact was low (59%); as such, only large estimated odds ratios reached significance, as seen above.

**Conclusions:** Stakeholders were near-universal in their belief that CHWs can improve HIV care engagement, but these benefits were not evident in the data from the full patient cohort. To improve outcomes, it is critical to ensure that all patients are connected with a CHW at initiation of care to promote more proactive, preventative forms of support. Future efforts should focus on clear communication, consistent oversight, and sustained cooperation on tasks across stakeholder groups.
Poster Presentations
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<td>Berendam Stella Basic</td>
<td><a href="mailto:stella.berendam@duke.edu">stella.berendam@duke.edu</a></td>
<td>Kinetics of Antibody Development, Functionality, and Breadth in SHIV.C.CH505 375H dCT-infected Infant Rhesus Macaques with Delayed ART Treatment</td>
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<td>Borges* Monica SBS</td>
<td><a href="mailto:monicaeb@live.unc.edu">monicaeb@live.unc.edu</a></td>
<td>Developing a predictive model for HIV clinical care disengagement</td>
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<td><a href="mailto:fb75@duke.edu">fb75@duke.edu</a></td>
<td>Identifying Immune Correlates of Time to Viral Rebound for Infant Rhesus Macaques</td>
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<td>Deng* Machao Basic</td>
<td><a href="mailto:machao.deng@duke.edu">machao.deng@duke.edu</a></td>
<td>Using Machine Learning in Pharmacokinetic and Pharmacodynamic Modeling of Anti-HIV Microbicide Performance</td>
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<td>Induction of neutralizing antibody (nAb) responses by immunization with soluble native-like HIV envelope trimer vaccines (SOSIP) in infant rhesus macaques</td>
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<td>Validation of biomarkers for estimating HIV-1 incidence</td>
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<td>Mathematical modeling of autologous antibodies impact on the time to viral rebound following ART interruption in postnatally SHIV-infected infant rhesus macaques</td>
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<td>Patient perspectives on the Helpfulness of a Community Health Worker program for HIV care engagement in Kilimanjaro, Tanzania.</td>
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<td>Cytomegalovirus glycoprotein B-specific antibody repertoire isolated from naturally-infected and V160 vaccinated individuals</td>
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<td>Yu*</td>
<td>Yahe</td>
<td><a href="mailto:yyu29@ncsu.edu">yyu29@ncsu.edu</a></td>
<td>Impact of Maternal HIV Infection on the Respiratory Microbiome of Infants</td>
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*Summer Intern project
Background: A successful pediatric HIV remission/cure strategy, especially in postnatally infected children, will likely require combination of ART with immune-based interventions that target HIV replication, limit the size of virus reservoirs, maintain virus suppression, and delay time to virus rebound. A previous small study reported that the development of HIV-specific antibodies in infants who started ART early delayed virus rebound following treatment interruption, suggesting that elicitation of HIV-specific antibodies in ART-treated infants could impact time to virus rebound. Most infants infected postnatally during the breast-feeding period do not start ART early due to delayed diagnosis. The kinetics of HIV-specific antibody response and their potential impact on virus rebound have never been studied in the setting of postnatal HIV transmission. To address this question, we used previously developed infant rhesus macaque (RM) model of breastmilk transmission with late ART therapy.

Objective: The primary goal is to define the kinetics, specificity, breadth, and antiviral functions of HIV-specific antibody responses in an infant RM model of postnatal HIV infection with late ART initiation.

Methods: Ten (n=10) infant RMs were orally challenged with SHIV.C.CH505 375H dCT and daily triple ART was initiated at 8-week post-infection (wpi). ART was interrupted after 52 weeks (ATI) and virus rebound was monitored by viral RNA detection in infant plasma. Envelope (Env)-specific antibody levels in infant plasma were measured against the autologous virus CH505 T/F gp120 and MN gp41. Meanwhile, infant plasma antibody specificity and breadth against cross clade HIV peptides were assessed using luminex-based assay. Infant plasma antibody neutralizing and non-neutralizing functions (ADCC and ADCP) were evaluated at time points pre-ART, during ART, and ATI.

Results: All infant RMs established plasma viremia with median viral loads at peak (2wpi) and immediately prior to ART were ~500,000 and 100,000 copies/ml, respectively. HIV Env-specific antibodies were first detected at 4wpi and following ART initiation (8 wpi) there was a significant decline in gp120- and gp41-specific antibodies, 89.7% and 88.5%, respectively. However, the antibody levels remained stable during ART until virus rebound/ATI. Infant plasma antibodies showed broad specificity and breadth against heterologous HIV Env peptides even while on ART. Upon ATI, virus rebound was observed in 9 of 10 infants (range, 7-35 days after ATI) with 5 of 10 infants developed autologous neutralization including 1 infant that did not rebound. Further assessment using purified IgG from infant plasma demonstrated limited neutralization and ADCC activities at pre-ART, during ART, rebound, and post-ATI. Infant plasma antibody from time point pre-ART, during Art, and ATI also mediated robust ADCP activity against CH505-gp120-coated beads.

Conclusions: Our results demonstrate that SHIV-infected infant RMs with late ART initiation are able to generate virus-specific antibody responses with broad specificity and breadth. Additionally, SHIV-infected ART-treated infant RMs continue to develop and maintain neutralizing and non-neutralizing antibody functions even while on ART. In future work, we will determine the Env-specific antibody half-life in infant plasma and define viral evolution that confer immune escape to autologous neutralization in postnatally SHIV-infected infants following long-term ART discontinuation. Overall, this study will inform the development of strategies to augment HIV-specific antibody responses in ART-treated infants to reduce the size of the viral reservoir and delay viral rebound following ART interruption.
Developing a predictive model for HIV clinical care disengagement

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. Here, we present an EHR-based predictive model that incorporates demographics, clinical history and health utilization behavior to identify persons at risk for disengagement from HIV care.

Methods
The outcome of interest, disengaging from care, is defined as not visiting the HIV clinic for 12+ months after previously being in care. Data came from the Duke HIV clinic spanning 2014-2018, and one year of data was used for each patient. 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 46 years; 72% male; 58% Black) were included in analysis. 39 candidate variables included demographics, mental health and STI diagnoses, substance use, and visits to the ER, hospital, and HIV clinic. Predictor variables positively associated with disengaging from care include number of positive gonorrhea or chlamydia tests; number of recent syphilis tests; ever being diagnosed with syphilis; a positive amphetamines test; and schizophrenia diagnosis. Predictors negatively associated with disengagement from care are higher age; number of gonorrhea/chlamydia tests; 2+ emergency visits; 1+ hospital admissions; depression diagnosis; and visiting the HIV clinic in each half of the year. A logistic regression model using these predictors for the testing set results in an AUC of 0.808.

Conclusions
A combination of demographic, STI/mental health diagnosis, and health behavior variables are useful for identifying PLWH in care who are at risk of disengaging. Future iterations of the model will incorporate data on structural barriers to health access. With HIV clinic visits in the model, emergency department and hospital visits still offer insight about the outcome.
Identifying Immune Correlates of Time to Viral Rebound for Infant Rhesus Macaques

Statistical analysis is carried out on experimental data to identify immune correlates that are predictive of time to HIV viral rebound. Data were acquired from 10 infant rhesus macaques, who were orally challenged with SHIV, given one-year of ART beginning at 8 weeks after infection, and then observed for viral rebound upon treatment interruption. 5 categories of potential immune correlates are investigated, including animal characteristics, viral load pre-ART, antibody response measurements, cell-associated RNA and DNA levels, and CD4 and CD8 cell counts. Univariate analysis is conducted using Cox Proportional Hazards (PH) models, while multivariate analysis is done by combining Cox PH models with LASSO regularization for variable selection. The findings suggest that (1) the positive area under the neutralization curve (which measures antibody neutralization capability) upon treatment interruption is a primary and significant predictor for time-to-rebound, and a higher value of this predictor seems to delay viral rebound; (2) peak GP41 antibody concentration pre-ART (which measures the intensity of antibody response) is a secondary predictor for time-to-rebound, and a higher value of this predictor is also associated with (though less significantly) delayed viral rebound.
Research Category: Basic/Translational

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Intravaginal rings (IVRs) can deliver multiple drugs, including anti-HIV microbicides. IVR performance was analyzed in deterministic compartmental modeling, focusing on: (1) using machine learning to (a) speed PK model computation times and (b) link PK measures in blood (easy to measure) to predict PK measures in target tissue for the drugs (hard to measure); and (2) PK measure sensitivities to uncertainties in model parameters. Using a large multiparametric simulation space, neural networks were created for (1) and accurately predicted output PK measures ($R^2=0.99$). In (2) a variance-based global sensitivity analysis was performed to calculate the sensitivity index for each input parameter corresponding to output PK measures. Greatest sensitivities were for drug loss rate from stroma to blood, drug clearance rate in blood, and histological dimensions of the epithelium and stroma of the vaginal mucosa. This analysis informs IVR design, helping account for population variation in IVR users.
Research Category: Basic/Translational

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Title & Authors: Induction of neutralizing antibody (nAb) responses by immunization with soluble native-like HIV envelope trimer vaccines (SOSIP) in infant rhesus macaques
Maria Dennis, Ashley Nelson, Celia LaBranche, David Montefiori, John Moore, Rogier Sanders, Koen Van Rompay, Genevieve Fouda, Kristina DeParis, Sallie Permar,

Background & Hypothesis: In 2018, there were 1.7 million new HIV-1 infections worldwide; ~160,000 of those infections were in children less than 15 years of age. In previous studies, HIV-infected infants were shown to make broadly neutralizing antibody (bnAb) responses in plasma at a faster rate when compared to that of adults. These bnAbs that have been isolated from pediatric HIV-infected patients are less somatically hypermutated (SHM) than those isolated from adults, suggesting that this response may be easier to elicit in early life. Previous studies assessing bnAb induction via immunization demonstrated that HIV Env GT1.1 SOSIP trimers can induce protective neutralizing antibody (nAb) responses in adult macaque vaccinees. In this pilot study, we hypothesized that immunization with the germline targeting BG505 GT1.1 SOSIP trimers would do a better job at inducing HIV bnAbs compared to the WT BG505 SOSIP in infant rhesus macaques.

Objective: The aim of this study is to assess the immunogenicity of BG505 GT1.1 SOSIP immunization in infant rhesus macaques and its ability to induce CD4bs bnAb precursors.

Methods: Two groups of 6 macaques were immunized with WT BG505 or GT1.1 mutant SOSIP, at 0, 6, and 12 weeks of age. At week 26 and 52 of age, both groups were boosted with WT BG505 SOSIP. The adjuvant used for all immunizations is 3M052-SE. To assess SOSIP trimer immunogenicity between the two regimens, we measured the magnitude of binding IgG responses against the BG505 wild-type (WT) and GT1.1 mutant trimer using quantitative ELISA. We defined the concentration of binding IgG responses using a rhesus b12 mAb of known concentration as a standard. A reporter cell-based plasma neutralization screening strategy was used to determine whether early precursors of CD4bs bnAbs had been elicited by the immunogen.

Results: WT and mutant BG505-specific IgG ELISA results demonstrated similar IgG binding responses over time as to what has been observed with previous immunogen strategies in infant macaques. The peak IgG magnitude was reached at 14 weeks’ post-immunization. Autologous tier 2 virus neutralization was achieved in 12 of 12 monkeys at week 28 post-immunization (after 4 immunizations) and enhanced at week 52 post-immunization for 4 of 12 monkeys. 3 infant macaques in the GT1.1 mutant group developed some plasma neutralization breadth by 54 weeks post-immunization. Moreover, 2 of the 3 aforementioned infant macaques exhibited a neutralization signature reflective of CD4bs precursor bnAb development. These results suggest that multiple immunizations with GT1.1 SOSIP could strengthen antibody neutralization function.

Conclusions: As more vaccine strategies are being developed, elicitation of broadly neutralizing antibodies remain a major goal for vaccine efficacy, and ideally, development of protective immunity should be targeted prior to adolescence. Our preliminary results show that a multi-dose HIV Env SOSIP trimer immunization regimen can initiate precursor bnAb development in infant rhesus macaques and should be considered for future HIV immunization strategies aimed to elicit protective antibodies in pre-adolescence, before sexual exposure risk begins.
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Structural characterization of HIV-1 Env V3-glycan DH1030-lineage bnAbs induced by macaque BG505 SHIV infection

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Background: Antibody DH1030.1 was isolated from rhesus macaques infected with SHIVs bearing transmitted-founder BG505 Env (BG505.T332N) as part of a 6-member bnAb lineage (DH1030). DH1030 mAbs had N332- and GDIR motif-dependent neutralization, and neutralized up to 17% of 119 heterologous tier 2 HIV-1 isolates. DH1030 lineage Abs used macaque VH3-al, whereas DH270 used VH1-2, but DH1030 lineage Abs encoded G56R mutation that was associated with neutralization breadth, similarly to G57R in DH270 V3-glycan bnAb isolated from an HIV-1-infected human. Here, we compared the structural properties of macaque DH1030 and human DH270 V3-glycan bnAbs.

Methods: Antigen binding fragments (Fab) of the DH1030 antibody were recombinantly expressed and purified. The Fab was mixed with the HIV-1 Env CH848.3.D0949.10.17.DS.DT SOSIP trimer in a molar ratio of 6 Fab : 1 Env trimer. Negative Stain electron microscopy (NSEM) and cryo-EM were used for determining structures of the DH1030 antibody bound to HIV-1 Env. The structure of the DH1030 Fab was determined by X-ray crystallography.

Results:
(1) Low resolution 3D reconstructions from NSEM data showed DH1030 bound at the HIV-1 Env V3-glycan supersite with antibody footprint overlapping with those of V3-glycan antibodies such as DH270.6 and PGT128.
(2) A 6.0 Å resolution cryo-EM structure of the DH1030 bound complex was solved. Despite the moderate resolution of the structure, critical elements of the epitope, including the Env V1 and V3 loops, glycans 156, 301, 332 and 442 were reasonably well-resolved. Upon fitting to the previously determined cryo-EM structure of DH270.6 bound to the same Env construct these epitope regions could be unambiguously defined.
(3) An X-ray crystal structure of the DH1030 Fab was solved at 1.8 Å resolution.
(4) Docking the high-resolution structure of the DH1030 Fab into the cryo-EM map of the DH1030-Env complex allowed unambiguous definition of the Env-interactive, complementarity determining regions (CDR) of the antibody.
(5) DH1030 bound the HIV-1 Env with an approach angle that was similar to that of DH270.6.
(6) The Env V1 loop in the DH1030-bound Env adopted a conformation similar to the V1 loop in DH270.6-bound Env. This conformation was distinct from the V1 loop conformation observed in the structure of the DH270 UCA-Env complex.
(7) DH1030 contacted the conserved GDIK region of the Env V3 loop via its CDR H2 loop. Similar to the DH270.6 antibody, the DH1030 CDR H3 loop made extensive contact with glycan 332. The CDR L1 loop made peripheral contact with glycan 442. Although glycans 156 and 301 were visible in the density, the antibody did not contact these glycans.

Conclusions: These studies confirm that antibody DH1030 targets the V3-glycan epitope and its mode of Env recognition is structural similar to the human V3-glycan bNab DH270.6.
Accurate estimates of HIV-1 incidence (the number of new infections over time in a population) is a crucial component of implementing and evaluating prevention strategies. Previous study using discriminant functional analysis had identified a set of 4 biomarkers to classify recent or longstanding HIV infection (Seaton, Vandergrift et al. JCI Insight, Dec 2017). These biomarkers included clade C gp140 IgG3, transmitted/founder clade C gp140 IgG4 avidity, clade B gp140 IgG4 avidity, and gp41 immunodominant region IgG avidity. In this study we validated this model of 4 biomarkers using a separate longitudinal cohort data, and obtained 85% accuracy and 20% false recent rate when using all data with multiple time points per participant, and 82% accuracy and 25% false recent rate when using one randomly selected recent and longstanding time point per participant. We also discovered additional models with subsets of 3 biomarkers that perform better or as well as the original model using existing data that come from either the original data or combined with the new data. However, no universal model was able to be identified at this moment. Since the two data sets come from two separate regions of cohorts, we suspect tests tailored to different geographic regions and strains of HIV may be more accurate. Univariate analysis on the new data set also suggests that there may be better biomarkers for this patient cohort, but additional analyses are needed.
Abstract

**Background:** HIV is one of the leading causes of death in Rwanda, disproportionately affecting women across all age groups. Access to antiretroviral therapy is now widely available in Rwanda, but there continues to be substantial barriers to accessing HIV care. HIV-related stigma and discrimination is highly prevalent in women living with HIV (WLWH) in Rwanda, with important implications for hindering care engagement. To date, no studies have examined the subjective experiences of stigma among WLWH in Rwanda. Thus, we conducted a qualitative study with thirty-three WLWH to gain a deeper understanding of the stigma experienced by the WLWH in Rwanda.

**Methods:** We conducted semi-structured focus groups interviews with thirty-three women in four different locations in Rwanda. We interviewed 8 participants from the urban city of Kabusunzu, 8 participants from the urban city of Kicukiri, 8 participants from the rural village of Tare, and 9 participants from the rural village of Shyorongi.

**Results:** Through thematic analysis, the following four themes emerged: dehumanizing language, role of society/relationships, making time for motherhood, and overcoming power of stigma. Dehumanizing language was prevalent with people in the community often referring to WLWH as “animals or “corpses” who “take the medicine fed to the pigs” and whose homes are referred to as “cemeteries”. This type of dehumanizing language was prominent in creating cultural rifts during the Rwanda genocide, which contributes to its strong impact on WLWH in their decision-making related to HIV care. Exclusion from roles in society/relationships was also a common theme, as stigma was experienced in both rural and urban settings, with each setting presenting its own unique challenges. For example, one participant living in a rural village stated “In town you find that things are a bit normal but in village, when you pass by, they say, they are passengers awaiting for their bus (death) and you feel strongly ashamed in your heart.” In order to overcome these experiences of stigma, the participants found comfort in focusing on motherhood and the wellness of their children, which were motivators for engaging in care. Other efforts at overcoming stigma included participating in formal support groups and by making decisions to disclose to individuals who were anticipated to be trustworthy.

**Conclusion:** In the Rwandan context, it is crucial to understand the use of dehumanizing language. A deeper exploration on how the remnants of polarizing language can be observed today may inform the development of interventions to ensure WLWH have the appropriate resources to overcome stigma. Additionally, further research is needed to explore the role of society and relationships in WLWH in order to develop community resources aimed at decreasing the occurrence of enacted stigma. WLWH identified motherhood as a motivator in engagement of care. More research is needed to explore the role of motherhood in fostering resiliency.
Integration of the proviral DNA intermediate into the host cell genome normally represents an essential step in the retroviral life cycle. While the reason(s) for this requirement remains unclear, it is known that unintegrated proviral DNA is epigenetically silenced. Here, we demonstrate that human immunodeficiency virus 1 (HIV-1) mutants lacking a functional integrase (IN) can mount a robust, spreading infection in cells expressing the Tax transcription factor encoded by human T-cell leukemia virus 1 (HTLV-1). In these cells, HIV-1 forms episomal DNA circles, analogous to hepatitis B virus (HBV) covalently closed circular DNAs (cccDNAs), that are transcriptionally active and fully capable of supporting viral replication. In the presence of Tax, induced NF-κB proteins are recruited to the long terminal repeat (LTR) promoters present on unintegrated HIV-1 DNA, and this recruitment in turn correlates with the loss of inhibitory epigenetic marks and the acquisition of activating marks on histones bound to viral DNA. Therefore, HIV-1 is capable of replication in the absence of integrase function if the epigenetic silencing of unintegrated viral DNA can be prevented or reversed.
Title: Mathematical modeling of autologous antibodies impact on the time to viral rebound following ART interruption in postnatally SHIV-infected infant rhesus macaques

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Antiretroviral therapy (ART) effectively suppresses HIV plasma viremia. However, ART interruption is often followed by viral rebound that returns plasma viral loads to pre-therapy levels. Time to viral rebound can be highly variable and several biomarkers have been identified to influence time to virus rebound, including the size of the latent reservoir, the level of CD4+ T cells and the timing of ART initiation (early vs late). Here, we focus on the role of the neutralizing antibody responses in delaying the time to virus rebound in postnatally SHIV-infected infant rhesus macaques (RM) following ART interruption. We develop a stochastic mathematical model of within-host, post-treatment dynamics in postnatally infected infant rhesus macaques. In addition to autologous neutralizing antibody data, we incorporate information on the latent reservoir size, the levels of CD4+ T cells, the time of treatment initiation and the binding antibody response. We parameterize our model using experimental data and literature-derived values and perform a sensitivity analysis to investigate the role of the neutralizing antibody response on the time to viral rebound.
Structural characterization of autologous Tier 2 neutralizing antibody DH1025.2 elicited by vaccination of rhesus macaques

Manne, Kartik; Edwards, Robert J; Tilahun, Kedamawit, Mansouri, Katayoun; Haynes, Barton F.; Saunders, Kevin; Acharya, Priyamvada

**Background:** Induction of protective antibody responses remains a challenge for HIV-1 vaccine design. Structural characterization of antibodies elicited by vaccination in animal studies can provide useful information on vaccine outcomes. Here we describe the structural characterization of antibody response elicited by vaccination of rhesus macaques with an engineered stabilized soluble HIV-1 envelope (Env) trimer derived from the HIV-1 primary isolate CH505 transmitted founder (TF).

**Methods:** Antigen binding fragments (Fab) of antibodies were recombinantly expressed and purified. Negative stain electron microscopy (NSEM) and cryo-electron microscopy (cryo-EM) were performed for determining structures of Env bound to Fab. Map sharpening and density modification methods were applied to improve the cryo-EM reconstruction. Coordinate fit was performed by iterative manual building in Coot, and by refinement of the modeled coordinates in Phenix and within the molecular dynamics-based platform in Isolde.

**Results:**
1. Low-resolution 3D reconstructions were obtained from NSEM data for complexes of HIV-1 Env SOSIP trimer bound to DH950 or DH1025.2 Fab. Both structures showed a single Fab bound to the HIV-1 Env trimer. The two antibodies bound Env with overlapping footprints and orientations that appeared nearly identical.
2. Cryo-EM reconstruction of DH1025.2 Fab bound to HIV-1 Env CH505.M5.G458Y.SOSIP revealed 3 Fabs bound to the HIV-1 Env trimer. A 4.8 Å resolution reconstruction of the complex obtained by applying C3 symmetry allowed resolution of the antibody complementarity determining regions (CDRs) and the Env epitope.
3. A key contact was made with glycan 156 with the glycan moiety bound in a cleft formed by the CDR L1 and CDR L3 loops of DH1025.2.
4. The long CDR H3 loop of DH1025.2 interacted with the conserved GDIR motif in the V3 loop. The tip of the V1 loop around glycan 137 was nestled in a shallow cleft formed by the CDR H3 and CDR L3 loops, with the glycan 137 visible in the electron density and directed away from the antibody.
5. Structural comparison of DH1025.2 and the DH270 lineage bnAb DH270.6 binding to Env showed difference in binding regions although both antibodies contacted the conserved GDIV/K region in the V3 loop. DH270.6 Fab binds to the V3-glycan epitope, whereas DH1025.2 Fab is shifted more towards the V1 base.

**Conclusions:** Structural determination first by NSEM to obtain low-cost, fast turnover and low-resolution structures, followed by cryo-EM to obtain high-resolution definition, provides a two-tiered feedback system for rapidly obtaining detailed characterization of interactions made by antibodies elicited during vaccination. Here structural characterization of Env interactions of antibody DH1025.2 revealed an epitope centered around glycan 156 of the V1 loop while also contacting the conserved GDIR motif on V3. The structure of the V1 loop bound to the antibody provides a molecular explanation for why DH1025.2 is ineffective against longer V1 loops.
Background: In our previous work, we presented a latent class model that can predict an HIV clinic patient’s risk of disengagement from care solely by classification into one of three classes of healthcare utilization. We hypothesize that aggregate indicators of a patient socioeconomic status is independently associated with their probability of classification into one of the patterns of health behaviors. We also describe how class membership affects health utilization patterns over time.

Methods: We analyzed the behavior of patients with HIV at the Duke Adult Infectious Disease Clinic between 2009-2013 across three previously identified latent classes (Adherent, Non-Adherent, Sick). Social Deprivation Index (SDI) scores, an aggregate score of seven factors associated with socioeconomic standing, were assigned to each patient based on their address of residence. In cases where address data were not available, we imputed SDI scores based on their county of residence using the K-nearest neighbor algorithm. We then fit a logistic regression model to assess the association of patient-level covariates of interest to assess their association with class membership. The following variables were incorporated into the analysis: SDI as a binary variable (below the mean vs. above the mean), age, sex and race. Second, we estimated the Latent Transition Analysis to study how the social deprivation index score, patient age, and its interaction, affect the odds of patients to transition from one class to another class across time.

Results: A total of 2019 patients were included in our analysis. The static behavior indicates that patients with worse demographic conditions (High SDI score) were more likely to be in the Sick class (odds ratio, 1.67; 95% confidence interval, 1.20-2.34) relative to other patients in the cohort. Also, young patients (age < 40 years) were more likely to be in the Non-Adherent class (odds ratio 2.35; 95% confidence interval, 1.70-3.28) relative to other patients in the cohort. In the first year for follow up, persons with higher SDIs were more likely to transition to the “Sick”, independently of their class, compared to persons with lower SDI scores. In the following years, their dynamic behavior of patients with worse demographic conditions was very stable. Finally, patients that are young and have worse demographic conditions were more likely to transition to the Non-Adherent class across the four years.

Conclusions: The effect of having worse demographic conditions and being a younger patient are crucial to understand they dynamic behavior of patients across our three latent classes (Adherent, Non-Adherent, Sick). The understanding of these patterns is very important to design more targeted treatments across the three groups in order to avoid people falling out of care and improving their quality of life.

Keywords: health care utilization; HIV care continuum, HIV engagement in care, latent class analysis, latent transition analysis.
Background: Community health workers (CHWs) are members of a community who receive basic training in the prevention and treatment of diseases. CHWs often engage in task-shifting, adopting some roles traditionally performed by health professionals to reduce the human resource burden in overtaxed health systems. In Tanzania, the Community-Based HIV Services (CBHS) program employs thousands of trained CHWs throughout the nation to support HIV testing, linkage to treatment, patient education, and care engagement at HIV clinics. In the Kilimanjaro region, CBHS workers at clinics aim to have an introductory meeting with all patients newly initiating HIV care, and then provide ongoing follow-up to support care engagement. Despite the program’s size and scope, few evaluations have been undertaken to assess its acceptability among patients, or it’s potential impact on HIV outcomes.

Methods: We enrolled 80 people living with HIV who were newly initiating HIV treatment at 3 urban clinics in Kilimanjaro, Tanzania to better understand their experiences with the CBHS program. New patients were identified by clinic nurses and referred to study staff to complete informed consent and a structured baseline survey. Participants were then contacted to complete a second follow-up survey 3 months later. The baseline survey included demographic and background information; the 3-month survey assessed care engagement, level of contact with the CBHS worker, and four open-ended qualitative questions examining: 1. patient experiences with the CBHS program, 2. level of connection with the CBHS worker, 3. perceived helpfulness, and 4. recommendations for program improvement.

Results: The mean age of participants was 36 years with majority (74%) being women. Among the 80 patients enrolled, only 23 (29%) were ever connected with a CBHS worker. Among these 23 patients, most believed meeting with the CBHS worker was helpful and described feeling personally connected. Patients described the CBHS workers as providing emotional support that helped them to accept their HIV diagnosis, and adherence support to encourage clinic attendance and medication adherence. Barriers to personal connection included lack of follow up after the initial meeting and lack of depth in conversations. Although, there was overall satisfaction with the program, suggestions for improvement included the need for closer follow-up by CBHS workers and expanding the program to reach more individuals living with HIV (e.g., those in the community who were not attending clinic). Further, participants reported a need for advocacy among people living with HIV and forming a community to support each other. There were also suggestions for the program to include assistance for financial and practical support for transportation, food and medication access.

Conclusions: Results from this study demonstrate high CBHS program acceptability among people living with HIV. Community health workers effectively provide emotional support and education to meet the psychosocial needs of people living with HIV, help to facilitate treatment adherence, and reduce stigma associated with status disclosure to prevent transmission. By virtue of their familiarity with the community culture, CBHS workers are a strong complement to HIV services, reduce gaps in the continuum of care delivery, and relieve the burden on overtaxed healthcare professionals. Findings from this study elucidate factors to inform the improvement or development of the CBHS programs for HIV service delivery, including the need for improved oversight to ensure adequate patient follow-up.
Persistent Elevation of Liver Transaminases Following HCV Virologic Cure Among HCV Mono-infected and HIV/HCV Co-infected Adults

**Background.** Approximately 10-30% of individuals living with human immunodeficiency virus (HIV) are co-infected with hepatitis C virus (HCV). These individuals experience higher rates of liver disease and mortality compared to HCV mono-infected individuals, and some demonstrate persistent elevation of liver transaminases (LEE) despite HCV sustained virologic response (SVR). Risk factors of LEE and long-term clinical implications, specifically among HIV/HCV co-infected individuals compared to HCV mono-infected individuals, remain unclear.

**Methods.** We conducted an exploratory, retrospective cohort study among HIV/HCV co-infected and HCV mono-infected patients at Duke University Health System between 2013–2017 with a documented direct-acting antiviral regimen and SVR, defined as undetectable HCV RNA viral load at least 10 weeks after end of treatment. LEE was defined as alanine aminotransferase (ALT) or aspartate transaminase (AST) elevation above the upper limit of normal (35 IU/L for males and 25 IU/L for females) in those patients achieving SVR. Demographic and clinical characteristics of mono- and co-infected patients were compared using Mann-Whitney for continuous variables and Fisher’s exact test for categorical variables. We used variable selection techniques to identify risk factors of LEE, and multivariable logistic regression to assess the relationship between HIV/HCV co-infection and LEE following SVR. A longitudinal mixed effects model was used to explore changes in ALT over time among HIV/HCV co-infected and HCV mono-infected patients.

**Results.** Among 706 patients with HCV included in the study, 35 had HIV co-infection. The median age of patients was 59, 56% were male, and 15% had a pre-treatment cirrhosis diagnosis. Compared to HCV mono-infected patients, HIV/HCV co-infected patients were more likely to be African American (80% vs. 47%) and had a higher distribution of model for end-stage liver disease scores. Risk factors selected included pre-AST and male sex. There was no statistically significant increase in odds of LEE among HIV/HCV co-infected patients compared to mono-infected patients (1.73 [0.43- 6.96]). There was also no significant difference between the two groups in ALT trajectories over time (p=0.66).

**Conclusions.** There was no significant increase in odds of LEE among HIV/HCV in this cohort. Due to the limited number of HIV co-infected patients and exploratory nature of these analyses, more study is needed to determine the true relationship between HIV co-infection status and persistent elevation of liver transaminases.
Research Category: Clinical

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Title: Connectome: HIV-Associated Neurocognitie Disorders (HAND)

Human Immunodeficiency Virus (HIV) affects more than 40 million people worldwide. HIV infection enters the brain shortly after infection and can cause HAND (in approximately 35%-50% of HIV+ patients). Hand is difficult to diagnose in an outpatient settings due to the requirement of a detailed neuropsychological performance testing (which take about three hours).

In our presentation, we will discuss how to use collected behavioral and MRI data in predicting whether or not a patient has HAND. The data was fed into different Machine Learning algorithms.
Research Category: Basic/Translational

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Human Cytomegalovirus (HCMV) is the most common congenital infection in infants worldwide. Prevention of HCMV infection is challenging due to the factors of high prevalence of the virus in the population, mostly asymptomatic infection, and inability of natural immunity to prevent reinfection. Development of a CMV vaccine has been assigned to tier 1 priority from the National Institutes of Medicine for over 20 years, but the effort has been hindered by poor understanding of the correlates of protection. Glycoprotein B (gB), the second most abundant protein in the virion envelope, is required for virus infection. Both neutralizing and non-neutralizing antibodies to gB develop during natural infection. The most promising HCM vaccine candidate to date, the gB/MF59 subunit vaccine, has shown efficacy in the clinic with about 50% protection against acquisition in seronegative women. Antibodies capable of binding to cell-associated gB have been shown to be a correlate of protection in the gB/MF59 study.

This study is designed to characterize the repertoire of non-neutralizing gB-specific monoclonal antibodies (mAbs) generated following natural HCMV infection or vaccination with a replication-defective HCMV vaccine (V160) developed by Merck. We analyzed 22 mAbs from 5 vaccinated and 24 mAbs from 3 naturally infected individuals. The antibody binding specificity was measured by multiplex ELISA to gB domains AD-1, AD-2, AD-4 and AD-5. None of the vaccinees mAbs mapped to a specific domain, whereas in naturally infected individuals, 30% were directed to AD-4 and 20% to AD-2. Interestingly, 100% of vaccinees mAbs bound above 50% of Cytogam (CMV HIG) binding to cell-associated gB, whereas only 62% of naturally-infected individuals’ antibodies bound above 50%. These results suggest that there are differences in the specificity of the repertoire of non-neutralizing gB-specific antibodies in vaccinated compared to naturally-infected individuals. Characterizing the differences in non-neutralizing antibodies elicited by vaccination and natural infection will allow us to shape a vaccine target that not only matches but exceeds natural infection.
Research Category: Basic/Translational

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In 2017, WHO statistics indicated that 1.8M children under 15 years of age are currently living with HIV worldwide. Most children were infected by their HIV-positive mothers during pregnancy, childbirth, and/or breastfeeding.

Our overall goal is to develop a Non-Human Primate (NHP) mathematical model of pediatric SHIV infection/ART treatment. This model can then be used to define the kinetics and predictors of viral rebound in postnatally-infected infants, and assess the impact of immune-based interventions to induce virus remission in infants. We want to understand how the virus behaves initially after infection, as well as how the viral dynamics in infants differ from adults. We build a simple mathematical model to describe initial SHIV infection and fit our model to initial viral dynamics in both infant and adult rhesus macaques. We estimate model parameters for each age group as well as for individual monkeys by utilizing a Bayesian hierarchical framework. We use Bayesian A/B testing to test for significant differences for our parameters across age groups. We show that the parameters with significant differences across age groups are related to the rate of rise of the viral load after infection as well as the peak viral load after infection.
Title & Authors: “Development of synthetic DNA-encoded dimeric IgA antibodies that potently neutralize rotavirus” Justin T. Steppe, Stephanie N. Langel, Jerry Chang, Elizabeth Parzych, David Weiner, Maria Blasi, Sallie Permar

Background & Hypothesis: Rotavirus (RV), a common enteric infection, is responsible for approximately 215,000 deaths in children under the age of 5, and is the leading cause of gastroenteritis-related hospitalizations worldwide. Therefore, increasing the levels of protective maternally-acquired sIgA antibodies in breast milk could reduce the risk of RV infection and extend the period during which infants are protected by maternal antibody transfer. We hypothesize that after injection and electroporation of optimized plasmid DNA with transgenes encoding a RV-neutralizing dimeric IgA (dlgA) antibody, locally transfected cells will produce high levels of dlgA antibodies in pregnant mice. Additionally, locally produced dlgA antibodies will passively transfer into breastmilk, providing protection against RV challenge in suckling neonatal pups.

Objective: To engineer plasmid DNA that expresses a RV neutralizing human monoclonal antibody RV (mAb#41) and passively transfers into breastmilk, providing protection against RV in suckling neonates.

Methods: We have engineered a plasmid expressing a murine dlgA version of a previously isolated human anti-RV neutralizing monoclonal antibody (mAb#41). Following transfection, the mAb#41-dlgA was characterized by ELISA, RV neutralization assay, size-exclusion chromatography, and electron microscopy. For further optimization to increase dlgA production, three separate plasmids (heavy, light, and J-chain) were used for transfection and the non-CDR portions of the sequence were optimized for antibody production. In vivo challenge studies were performed to validate our model. 129sv dams were infused with either 15mg/kg mAb#41-dlgA or PBS and their pups were inoculated with the Wa strain of human RV. We also included one dam that was infused with PBS and whose pups were challenged with PBS as a control.

Results: Transfection of 293T and RAMOS B cells resulted in high levels of both total IgA and J-chain binding IgA antibodies. We confirmed that mAb#41-dlgA binds to its cognate receptor, polymeric immunoglobulin receptor, and effectively neutralizes the human RV Wa strain. Further characterization by size-exclusion chromatography and electron microscopy showed that different antibody species are produced following transfection, including J-chain-containing monomeric, dimeric, and polymeric IgA. Optimization studies demonstrated that using three separate plasmids for heavy chain, light chain, and J-chain in addition to making specific sequence changes resulted in better production of dlgA after transfection. In vivo challenge studies showed that pups suckling from dams that received 15mg/kg mAb#41-dlgA were better protected against RV challenge compared to those suckling from dams that received PBS. For example, 16.7% of the pups born to the 15mg/kg mAb#41 treated dam exhibited clinical signs on day 1 post-inoculation with the Wa strain of RV. However, 83% of the pups born to the PBS treated dam exhibited clinical signs on day 1 post-inoculation with the Wa strain of RV. The pups born to the 15mg/kg mAb#41 treated dam also showed improved weight gain compared to pups born to the PBS treated dam. The average weight of pups born to the 15mg/kg mAb#41 treated dam increased from 2.56g to 2.72g from day 0 to day 1 post-inoculation, while the average weight of pups born to the PBS treated dam actually decreased slightly from 2.73g to 2.7g over the same time frame.

Conclusions: We demonstrated that our plasmid is capable of producing dlgA that potently neutralizes RV. We have also demonstrated that dlgA produced by our plasmid, when given to nursing dams, traffics to the breastmilk and provides protection to pups against RV infection. Current and future work involves assessing the ability of electroporated mAb41-dlgA plasmids to enhance RV-specific maternal antibody delivery via breastmilk in our mouse lactation model. Results from this work will guide the development of maternal immunization strategies for other pathogens like respiratory syncytial virus, influenza, and HIV, that improve passive transfer of dlgA antibodies into breastmilk.
Title & Authors: The role of maternal broadly neutralizing antibodies in mother to child transmission
Joshua J. Tu, Joshua A. Eudailey, Allison Thomas, Yvetane Moreau, Elena E. Giorgi, Celia C. LaBranche, David C. Montefiori, David R. Martinez, Genevieve G. Fouda, Feng Gao, Manish Sagar, Sallie R. Permar

Background & Hypothesis: Despite the worldwide availability of antiretroviral therapy (ART), around 150,000 pediatric HIV infections occurred in 2019. ART can dramatically reduce HIV mother-to-child transmission (MTCT) rate, but struggles to maintain drug adherence and to diagnose new maternal HIV infections are major barriers to preventing vertical transmission. Thus immunologic strategies to prevent MTCT, such as an HIV vaccine, are required to attain an HIV-free generation. The goal of HIV vaccine research has been to elicit broadly neutralizing antibodies (bnAbs), but our previous work has shown that postpartum transmitting mothers have higher bnAb activity than non-transmitting mothers. Additionally, we have identified a V3 glycan bnAb-resistant infant transmitted/founder (T/F) virus that was selectively transmitted by escaping the maternal plasma V3 glycan bnAb response. In this study we examine a larger cohort of women with high neutralization breadth to determine if certain maternal bnAb specificities drive the selection of infant T/F viruses.

Methods: Patient samples were selected from the Breastfeeding, Antiretroviral, and Nutrition Study (BAN) and the Center for HIV/AIDS Vaccine Immunology 009 (CHAVI009) cohorts (Malawi). The neutralization breadth of maternal plasma was tested in TZM-bl cells against an eleven virus global panel. Breadth was defined as neutralization at an ID50 greater than or equal to 50 for at least six of the eleven viruses tested. Additionally, samples that neutralized at least one virus at an ID50 of 120 or greater were mapped for bnAb specificity. The bnAb specificities tested were the CD4 binding site (CD4bs), V2 glycan, V3 glycan, and membrane-proximal external region (MPER) using panels of mutant pseudo-typed viruses (psvs).

Results: From the BAN cohort, 17 of 21 transmitting mothers and 28 of 42 non-transmitting mothers demonstrated neutralization breadth. From the CHAVI009 cohort, 1 out of 3 transmitting mothers and 17 out of 62 non-transmitting mothers demonstrated neutralization breadth. Patients with neutralization potency and available samples were tested for neutralization specificity, leaving us with a final cohort size of 7 transmitting and 21 non-transmitting mothers. Using HIV pseudoviruses (psv) that have mutations at epitopes targeted by bnAbs, we attempted to map women with broad and potent neutralization to these epitopes. Samples were considered mapped to a bnAb epitope if neutralization against a mutant psv was at least 2 fold lower than the wild type psv ID50. Six of 7 (85.7%) transmitting women were mapped, two to N276 CD4 CD4bs, one to the N160 V2 glycan, and two to the N332 V3 glycan. The sixth transmitting mother was mapped to both the CD4bs and the V3 glycan. Of the non-transmitting mothers, 7 of 16 (43.8%) were mapped. Four mothers were mapped to the CD4bs, one to the V2 glycan, and one to the V3 glycan. One non-transmitting mother was also mapped to both the CD4bs and V3 glycan epitopes. Our preliminary data show a trend for transmitting mothers to more frequently have a mappable bnAb specificity compared to non-transmitting mothers (OR = 7.1, p=0.09 by 2-sided Fisher exact test).

Conclusions: In this study, we show a trend that in most transmitting women with broad plasma neutralization responses, broad neutralization is mediated by a single specificity. This suggests that developing a monoclonal maternal bnAb may not be sufficient to prevent MTCT and that multispecific bnAb activity in plasma may be necessary to protect against the development of viral escape variants. We are currently mapping additional maternal samples to increase our sample size and confirm these results.
Kinetics of Vaccine-Elicited antibodies in HIV-exposed infants from Botswana
Uffman, Emilie, Shuk Hang (Grace) Li; Ganga Moorthy, MD; Rebecca R. Young, MS; Genevieve Fouda, MD, PhD; Matthew S. Kelly, MD, MPH

Background: Respiratory infections, such as respiratory syncytial virus (RSV) and pneumococcal pneumonia, remain the leading causes of lower respiratory tract infections and mortality among children globally. HIV-exposed, uninfected infants are particularly susceptible to respiratory infections and have higher early childhood mortality than HIV-unexposed infants. Factors that could contribute to this increased susceptibility of HIV-exposed uninfected children include feeding practices, maternal illness, and suboptimal immune responses to vaccination. In this study, we aim to determine the effect of HIV exposure on the immunogenicity of a pediatric vaccine panel in a cohort of infants in Botswana.

Methods: We obtained plasma samples from 74 children from Botswana at 0, 5, and 12 months of age. We measured their antibody responses against the 13 serotypes of \textit{S. pneumoniae} (PnPs) contained within 13-valent pneumococcal conjugate vaccine using an enzyme-linked immunoabsorbent assay (ELISA). A pediatric vaccine multiplex assay (PVMA) was used to detect antibody binding to a panel of bead-conjugated pathogens. Median fluorescent intensity (MFI) of the samples was measured. Bio-Plex Manager was used to interpolate concentrations from standard curves.

Results: The magnitude of the antibodies increased following vaccination and was higher at 5 months than at birth for all 13 serotypes of PnPs, diphtheria, pertussis, and \textit{Haemophilus influenzae} type B. However, antibody levels rapidly decreased and the levels at 12 months of age were significantly lower than at 5 months. Infants were born with antibodies against hepatitis B, tetanus, rubella, and RSV, however the antibody levels declined significantly from birth to 5 months of age. At 12 months of age, most infants had continued low antibody levels. However, some infants had an increase in antibody levels from 5 months of age, indicative of infection.

Conclusions: Our results indicate that infants from Botswana develop robust antibody responses following vaccination, but these antibodies wane rapidly during infancy. The clinical significance of this rapid decline is unclear. Vaccine strategies capable of inducing robust, durable antibody responses or an additional vaccine booster may be required to ensure protection from respiratory infections throughout childhood.
Research Category: Basic/Translational

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Pre-existing immunity to cytomegalovirus in cynomolgous and rhesus monkeys influences human CMV vaccine responses in preclinical models.  

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Development of a human cytomegalovirus (HCMV) vaccine is a Tier 1 priority by the National institutes of Medicine, as HCMV is the most common cause of congenital infection globally and a serious complication for transplant patients. Currently there is no vaccine or therapeutic available for treatment and the correlates of protection have remained elusive. A relevant preclinical model for testing HCMV vaccine immunogenicity are rhesus and cynomologous monkeys. However, a complication in using this model is the fact that species-specific CMV variants are endemic in non-human primate breeding colonies. We hypothesize that natural immunity to species-specific CMV in rhesus and cynomologous monkeys interferes with our ability to fully interpret HMCV vaccine immunogenicity.

A modified mRNA vaccine encoding HCMV gB and the pentameric complex packaged in lipid nanoparticles was delivered intramuscularly to groups of cynomologous macaques (n=16, cynoCMV+) and rhesus macaques (n=31, RhCMV+), each in low and high dose subgroups. The background pre-vaccination IgG binding responses to HCMV gB were initially high in both species. Yet, post 2nd HCMV mRNA vaccination a log increase in pentamer and gB antibody levels was detected. There was a particularly strong antibody response post vaccination to gB domain I in cynomologous macaques and gB domain II in rhesus macaques, suggesting a recall response. Both species exhibited highly neutralizing antibodies post 2nd HCMV mRNA vaccination in epithelial cells. HCMV-vaccinated cynomologous and rhesus macaques had significantly increased IgG binding responses to cell-associated gB after the second vaccination, but rhesus macaques showed no change from pre-vaccination antibody binding to cell-associated gB. ADCP responses against HCMV were detected only in rhesus macaques, but did not increase post vaccination. There was no ADCP activity pre or post vaccination for cynomolgous macaques.

Pre-existing anti-species-specific CMV antibodies in monkeys may inhibit our ability to assess the full humoral response to HCMV gB vaccines, in particular IgG responses against the rhesus CMV cell-associated gB protein. Species-specific CMV variants may contribute more pre-existing antibody interference to gB antibodies compared to pentamer, and cynomologous macaques may have less cross-reactive preexisting responses to gB compared to rhesus macaques. Due to interference of pre-existing immunity to cynomologous and rhesus CMV, we may be unable to fully assess non-neutralizing gB antibody function in these models, and this raises the question of whether vaccine interference will be observed in seropositive HCMV vacciness.
INTRODUCTION: More than 1 million infants are born annually to HIV-infected mothers worldwide. These HIV-exposed, uninfected (HIVEU) infants experience higher morbidity and mortality than HIV-unexposed (HU) infants in the same communities. Most of this excess mortality occurs during infancy and results from pneumonia. Recent studies suggest that the upper respiratory microbiome influences the risk of respiratory infections during childhood. Thus, understanding the extent to which the maternal respiratory microbiome is transmitted to infants could further knowledge of early-life colonization of the respiratory tract and elucidate a novel mechanism by which maternal HIV infection influences child respiratory health.

METHODS: We used clinical data and nasopharyngeal swab samples from a prospective cohort study of 139 mother-infant pairs in Botswana. Mothers and infants were enrolled at birth and followed monthly (0-6 months) or every two months (6-12 months) for the first 12 months of life. We selected all infant samples and the maternal sample from the birth visit for sequencing of the V4 region of the 16S ribosomal RNA gene. We used linear mixed models to assess the effect of maternal HIV status and breastfeeding on the composition of the nasopharyngeal microbiome. We compared overall microbiome composition between infants and mothers (own vs. others), based on Bray-Curtis dissimilarity and stratified by HIV exposure status and breastfeeding.

RESULTS: Of 139 infants included in these analyses, 40 (29%) were HIVEU and 99 (71%) were HU. The Shannon diversity of the nasopharyngeal microbiome was similar among HIVEU and HU infants (p=0.29), but HIVEU infants had higher Chao1 richness (p=0.04). The composition of the nasopharyngeal microbiome was also similar in HIVEU and HU infants. We observed a significantly lower dissimilarity between an infant’s microbiome and his/her own mother’s vs. other mothers’ microbiomes in both HIVEU (p<0.001) and HU (p<0.001) infants during the first year of life. Furthermore, we found that breastfeeding tended to be associated with less dissimilarity between an infant’s microbiome and his/her mother’s microbiome (p=0.08).

CONCLUSIONS: Maternal HIV infection does not have a substantial impact on the upper respiratory microbiome of infants. Our results provide evidence for respiratory microbiome sharing between mothers and infants or, alternatively, the effect of the household environment on the respiratory microbiome.
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