Abstract Book
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Abstracts
Abstract: 1

Virology of HIV Transmission

Female-to-Male Transmitted/Founder HIV-1 are Less Susceptible to Inactivation by Vaginal Microbiota Acid Metabolites than Non-Transmitted Strains

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Introduction. The majority of HIV infections result from heterosexual transmission typically established by a single transmitter/founder (T/F) virus; however the role of vaginal microbiota (VMB) acid metabolites in modulating HIV transmission originating from women is unknown. A major risk factor for HIV acquisition is bacterial vaginosis (BV). BV is associated with an increase in vaginal pH (>4.5) and a shift in the VMB acid profile typified by a dramatic decrease in lactic acid (LA, non-BV) and an increase in short chain fatty acids (SCFAs). Here, we investigate if T/F virus is less susceptible to inactivation by LA and BV-associated VMB acids than NT subtype B and C variants (p<0.013) that typically were inactivated by 104-fold or completely. VMB acid susceptibility of a male-to-female (Z3576) T/F was similar (p=0.12) for 1 of 3 NT donor variants.

Conclusions. VMB acid metabolites present in lactobacillus-dominated microbiota (non-BV) potently inactivate HIV in contrast to BV acids. Reduced susceptibility of T/F to VMB acids (including LA at threshold levels) may be a trait that enables survival of HIV shed into the vagina that could increase transmission probability from female-to-male or mother-to-child, during vaginal birth.

No conflict of interest

Abstract: 2

Modeling of HIV Transmission

HIV-infected macrophages can establish de novo infection after vaginal exposure

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Introduction: Vaginal exposure during heterosexual intercourse remains a primary source of HIV-1 transmission, and HIV can persist linked heterosexual transmission pairs. HIV infectivity was determined in TZM-bl cells.

Results. VMB acid combinations found in non-BV (with 100 mM LA) completely inactivated T/F variants in contrast to BV acids. At equimolar virucidal levels, HIV-1 subtype B T/F (RHPA, CH058) and subtype C female-to-male T/F (Z3618, Z331) were less susceptible to inactivation by LA (range 2.2 – 150 fold) and BV-associated VMB acids than NT subtype B and C variants (p=0.013) that typically were inactivated by 104-fold or completely. VMB acid susceptibility of a male-to-female (Z3576) T/F was similar (p=0.12) for 1 of 3 NT donor variants.

Conclusions. VMB acid metabolites present in lactobacillus-dominated microbiota (non-BV) potently inactivate HIV in contrast to BV acids. Reduced susceptibility of T/F to VMB acids (including LA at threshold levels) may be a trait that enables survival of HIV shed into the vagina that could increase transmission probability from female-to-male or mother-to-child, during vaginal birth.

No conflict of interest
in the male reproductive tract (MRT) despite antiretroviral therapy (ART). Infected T-cells and macrophages are present in HIV/SIV(+) semen and can initiate infection in vitro. Exposure to infected T-cells at the vaginal mucosa is capable of establishing infection in vivo. However, to our knowledge, the ability of HIV-1 infected macrophages to establish infection at vaginal mucosa in vivo has not been determined.

**Materials and Methods:** The bone marrow, liver, thymus (BLT) humanized mouse model of HIV-1 infection was used to investigate the capacity of infected macrophages and T-cells delivered at the vaginal mucosa to establish systemic infection. Humanized BLT mice (n=11) were vaginally exposed to human T-cells infected in vitro with HIV-1 JR-CSF or to cell-free virus. To investigate the ability of macrophages to establish de novo infection, two different experiments were conducted. First, CD4 T-cells and macrophages were isolated from the same donor and infected with the macrophage-tropic HIV-1 ADA isolate. Then, BLT mice (n=5) were vaginally exposed to either infected human monocyte derived macrophages (MDM) or autologous infected CD4 T-cells. In a separate experiment, BLT mice (n=3) were vaginally exposed to macrophages harvested from humanized myeloid-only mice (MoM) infected with HIV-1 CH040, a transmitted-founder virus that has been shown to infect both T-cells and macrophages (Honeycutt et al J. Clin. Invest. 2016). HIV-1 viral load and peripheral CD4 T-cell levels were monitored longitudinally, and HIV-1 DNA levels were determined in multiple tissue sites at the time of harvest.

**Results:** Both cell-free HIV-1 JR-CSF (5 of 6 mice infected) and HIV-1 JR-CSF-infected CD4 T-cells (5 of 5 mice infected) were able to establish de novo infection after a single vaginal administration (p=0.3613). Similarly, in vitro-infected MDM were able to establish infection in 5 of 6 mice after vaginal exposure. Infection, established by either infected CD4 T-cells or MDM, resulted in CD4 T-cell depletion in cervicovaginal lavage of infected mice. Vaginal exposure to macrophages directly isolated from HIV-1 CH040-infected MoM resulted in systemic infection of 2 of 3 mice exposed, compared to 5 of 6 mice exposed to cell-free HIV-1 CH040 (p=0.7186).

**Conclusions:** To our knowledge, our data represents the first demonstration that HIV-infected macrophages can establish de novo infection after vaginal exposure with comparable efficiency to infected CD4 T-cells. Additionally, this platform will be significant in the investigation of HIV preventive approaches targeting macrophage and T-cell mediated HIV transmission.

No conflict of interest

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**Abstract:**

**Unique phenotypic properties influence HIV-1 mucosal transmission fitness**

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**Background:** Heterosexual HIV-1 transmission requires the virus to penetrate the physical mucosal barrier to establish a systemic infection. In the vast majority of cases, infection is initiated by one, or a small number of donor transmitted HIV-1 clones. However, it is still not fully understood if the transmission bottle neck occurring in the recipient’s mucosa is a stochastic event or if certain HIV-1 phenotypes were actively selected. Here we present data evaluating the possible genotypic and phenotypic differences in a number of acute and chronic HIV-1 viruses that may influence mucosal transmission fitness.

**Methods:** Chimeric Env viruses from acute and chronic isolates were evaluated for host cell entry and receptor binding efficiency, sensitivity to entry inhibitors, and for replication fitness in PBMCs, T cells and macrophages. We also compared their transmission fitness across human penile and cervical explant tissue using multi-virus competition assays. Additionally we assessed the

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HIV-1 genetic diversity in the female genital tract and compared it to isolates from the blood by 454 sequencing of the envelope region.

Results: Acute and chronic HIV-1 had similar entry kinetics, sensitivity to entry inhibitors and replication fitness. In contrast we observed that acute isolates penetrate tissue, bind to DCs and establish infection in T cells more efficiently than chronic HIV-1. Chronic isolates were seen to remain and replicate mainly in the tissue. Interestingly higher transmission fitness of the acute isolates correlated with reduced numbers of conserved N-linked glycosylation sites on the envelope. Sequence analysis of the envelope revealed that HIV-1 in the female genital tract is more diverse while only one or a few HIV-1 clones are found in the blood during primary infection.

Conclusion: The majority of mucosally transmitted HIV-1 appears to be trapped in the tissue, possibly due to high levels of mannose binding proteins found in tissue and lectins expressed on epithelial cells. These sugar binding proteins may be responsible for a passive selection process of HIV-1 isolates with reduced glycans for transmission across mucosal tissues, while HIV-1 isolates with higher numbers of N-linked glycans get trapped in the tissue.

Introduction: EFdA (4’-Ethynyl-2-Fluoro-2’-Deoxyadenosine) is a new NRTI with antiretroviral potency several orders of magnitude higher than any of the current clinically used NRTIs. It has favorable toxicity profiles in vitro and in vivo, is resistant to degradation by adenosine deamination, does not inhibit human DNA polymerases α and β or mitochondrial polymerase γ, and effectively inhibits clinically important drug resistant HIVs. Using humanized BLT (bone marrow-liver-thymus) mice as a preclinical model to evaluate HIV prevention strategies, we investigated the potential of EFdA to prevent mucosal transmission of HIV at the two primary sites of HIV acquisition in women and infants (vagina and oral mucosa).

Methods: EFdA was administered orally to NSG mice and to humanized BLT mice. HIV inhibitory activity in serum, cervicovaginal secretions and saliva was evaluated 4 h after administration. EFdA ability to prevent vaginal and oral HIV transmission after multiple high-dose HIV exposures was evaluated using highly relevant transmitted-founder (T/F) viruses in BLT mice.

Results: After a single oral dose of EFdA we observed strong HIV inhibitory activity in the peripheral blood serum (p=0.0031), cervicovaginal secretions (p=0.0016), and saliva (p=0.0161) from EFdA-treated mice compared to untreated controls. These data indicate systemic distribution of active EFdA after a single oral administration and efficient penetration into the female reproductive tract and the oral cavity. Consistent with these results, a single daily oral dose of EFdA also resulted in efficient prevention of vaginal (p=0.0002) and oral (p=0.0031) HIV transmission after multiple high-dose HIV exposures to various T/F viruses in BLT humanized mice.

Conclusion: Our data demonstrated that EFdA efficiently prevents both vaginal and oral HIV transmission. Together with EFdA’s relatively low toxicity and high potency against drug-resistant HIV strains, these data support further clinical development of EFdA as a potential pre-exposure prophylaxis (PrEP) agent to prevent HIV transmission in women and their infants.

No conflict of interest
Abstract: 5

Epidemiology of HIV Transmission

Identifying growing clusters of recent, rapid HIV transmission to target prevention

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Background: Transmission network analysis, conducted using HIV sequence data, is a tool to identify clusters of HIV cases resulting from recent and rapid transmission. It may help identify social networks at the highest risk for ongoing transmission and can present opportunities for directing prevention resources. To date, transmission network analyses of national data in the United States have defined potential transmission pairs as cases with sequences with a genetic distance of ≤1.5% in pol. Although this threshold maximizes the identification of partners with a likely epidemiologic relationship, it allows for approximately 15 years of viral evolution and thus may still have high sensitivity for detecting transmission events that occurred many years ago. We compared growing clusters identified at a 0.5% threshold to those identified at a 1.5% threshold to determine whether the reduced threshold increased specificity for recent, rapid transmission.

Methods: For cases diagnosed during 2013–2015, we analyzed HIV-1 protease and reverse transcriptase sequences reported to the National HIV Surveillance System by 27 jurisdictions conducting Molecular HIV Surveillance. Transmission networks were generated at genetic distance thresholds of both 1.5% and 0.5% using HIV-TRACE (HIV TRAnsmission Cluster Engine, www.hivtrace.org). We assessed the number of clusters identified at each threshold, and identified clusters that grew by at least 5 cases during 2015. We then conducted molecular clock phylogenetic analysis using BEAST v.1.8 (Bayesian Evolutionary Analysis Sampling Trees, http://beast.bio.ed.ac.uk) with a strict molecular clock to infer the time of most recent common ancestor of the cluster and estimate the upper bounds of timing of transmission events for all clusters at the 0.5% threshold and a random sample of clusters at 1.5% threshold.

Results: During 2013–2015, of the 80,845 cases of HIV infection that were diagnosed in the 27 jurisdictions, 30,623 (37.9%) had HIV sequences available. Using a genetic distance threshold of 1.5%, these sequences formed 3413 transmission clusters, of which 73 grew by at least 5 cases; at 0.5%, there were 1923 clusters of which 13 grew by at least 5 cases in 2015. Molecular clock analysis demonstrated that the 13 clusters at 0.5% had been diversifying for a median of 4.4 years (range 1.6–8.0) compared with 10.5 years (range 6.2–16.6) for 13 clusters selected at random at 1.5%. For the 182 nodes in the 13 clusters at 0.5%, the median node age was 2.2 years (range 0.6–3.7), and 17.6% of nodes had ages of less than 1 year; for the 254 nodes in the 13 clusters at 1.5%, the median node age was 4.8 years (range 2.2–6.9 years), and 2.8% of nodes had ages of less than 1 year.

Conclusion: Transmission network analysis using a lower genetic distance threshold of 0.5% resulted in a smaller number of clusters that were more likely to represent recent, rapid transmission. Given limited public health resources, this approach may allow programs to effectively prioritize clusters for which intervention will have the greatest potential to reduce future infections.

No conflict of interest

Abstract: 6

Epidemiology of HIV Transmission

Increased ability of molecular surveillance data to describe HIV transmission in the United States

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Introduction: Molecular surveillance data can be used to (1) understand HIV transmission within and between populations, (2) identify growing clusters of HIV transmission, and (3) target timely and effective interventions to limit transmission. Collection of HIV nucleotide sequence data through the National HIV Surveillance System (NHSS) has expanded, with 27 jurisdictions funded for this activity during 2013–2017, compared with 11 jurisdictions in 2008–2012. A previous analysis at CDC used national surveillance data reported through 2012 to describe HIV transmission networks. We examined how completeness of sequencing data and transmission patterns may have changed since that time.

Materials and Methods: We analyzed data submitted to CDC through NHSS from 27 jurisdictions through December 2015. Using partial HIV-1 polymerase sequences reported for persons with HIV infection diagnosed in 2007–2015, we aligned all sequences, then conducted pairwise comparisons of all sequences to identify pairs with a genetic distance of ≤1.5% (i.e., potential transmission partners). We described characteristics of the transmission network, including the number of links and distinct clusters. We also calculated the percentage of sequences that were linked to at least one other sequence by demographic and risk characteristics, such as age, sex, race/ethnicity, and transmission category.

Results: Of 276,350 persons with HIV diagnosed during 2007–2015, 85,505 (31%) had sequences available for inclusion in the analysis, a substantial increase from the 41,549 received included in the previous analysis conducted in 2012. Among those with sequences, 39,985 (47%) were linked to at least one other sequence (increased from 32% in the prior analysis). The transmission network contained 128,876 links; among persons with any links, the median number of links was 3 [interquartile range (IQR): 1, 7], with a maximum of 103 links. There were 8,413 distinct clusters; the median cluster size was 3 sequences [IQR: 2, 4], with a maximum size of 172 sequences.

Conclusions: Improved reporting and completeness of nucleotide sequence data likely resulted in identifying a higher percentage of potential transmission partners, reducing the number of persons with no linkage information and improving CDC’s ability to understand HIV transmission patterns. Continued efforts are necessary to ensure timely and complete data to further increase the robustness of NHSS to detect growing HIV clusters and implement prevention strategies to halt disease spread.

No conflict of interest

Abstract: 7

Modeling of HIV Transmission

On the distribution of multivariant HIV-1 transmission events

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Background: Although 99 out of 100 sexual exposures to HIV-1 do not result in infection, when infection does occur, it is frequently established by multiple genetic variants, with
multiple studies reporting a multivariant infection risk of approximately 20%. Such a risk is impossibly high under models that assume each virus acts independently of all other viruses at the site of infection, and that all exposures are equally likely to establish infection.

**Material and Methods:** We begin with the assumption that, within the context of a single exposure event, all viruses are independent and (a priori) equally likely to establish infection. Here, independence implies (for example) that viruses are not clumped together, nor does the productive infection of a recipient target cell alter the probability that another virus will productively infect a target cell. These assumptions imply that the number of transmitted variants will follow a binomial distribution, parameterized by the number of virus particles and the a priori probability that each virus will be transmitted. We extend this simple model to allow for some exposure events to be high risk, while others remain low risk, where risk is defined as the probability that at least one virus is transmitted (ie, infection occurred). In the simplest mixture model, all exposures are either high or low risk. A more realistic extension allows a continuous range of transmission risk, where per-exposure transmission risk follows a Beta distribution.

**Results:** We show that a simple two-risk model, in which a very small minority of very high-risk exposures are almost certain to establish infection, can explain the discordance between low aggregate transmission risk but high rates of multivariant infection. For example, parameterizing the model as a mixture of binomials in which rare (<2%) high-risk exposures are 2-4 orders of magnitude more likely to establish infection relative to low-risk exposures yields an average risk of infection of 1/100, with 20% of infections established by multiple genetic variants. Such a mixture also diminishes the role of ‘viral load’ (modeled as the absolute number of viruses at the site of exposure) in predicting infection, such that increasing viral load results in a sub-linear increase in the probability of infection. This latter result is driven by the risk of infection in the high-risk group saturating near 1. The smoothed beta-binomial model similarly fits the data well, and further allows posterior estimation of exposure risk once the number of transmitted variants is known. Overall, multivariant transmission is indicative of relatively high-risk exposure relative transmission of a single viral variant.

**Conclusions:** Our models provide a simple analytical framework for studying rates of transmission and the expected number of transmitted variants and show that published data are consistent with simple models in which observed transmissions typically result from very high-risk exposure events, which make up a small minority of all exposure events in a population. One practical prediction of the model is that multivariant transmission may be used to identify individuals who were likely at relatively high risk at the time of exposure.

No conflict of interest

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**Abstract: 8**

**Transmission of HIV Drug Resistance**

**High rates of transmission of drug-resistant HIV in Aruba resulting in reduced susceptibility to the WHO recommended first-line regimen**

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**Introduction:** In Western countries emergence of HIV drug resistance has tremendously decreased and transmission of drug resistance has merely stabilized in recent years. However, in many endemic settings with limited resources rates of emerging and transmitted drug resistance are not regularly assessed. Aruba is a densely populated Caribbean island, which has an increasing number of new HIV diagnoses. We noted a
worrying rise in the detection of the resistance mutation K103N, which compromises the efficacy of the WHO-recommended first-line NNRTI-based (non-nucleoside reverse transcriptase inhibitor) regimen. Therefore, we investigated the population infected with this resistant variant and its transmission dynamics.

**Methods:** We performed a survey including all HIV-infected individuals who received resistance testing in 2010-2015 in Aruba. Transmitted HIV drug resistance was determined using WHO-criteria. Baseline characteristics were compared between individuals with and without baseline NNRTI resistance using chi-squared and Mann-Whitney U tests. A maximum-likelihood phylogenetic tree was constructed using the GTR-model. Transmission dynamics were investigated using advanced phylogenetic analyses. In a subset, baseline samples were reanalyzed using next generation sequencing (NGS).

**Results:** Baseline resistance testing was performed in 104 newly diagnosed untreated individuals (54% of all newly diagnosed individuals in 2010-2015). 86% were men, 39% were foreign-born and 22% had AIDS at diagnosis. Of all newly diagnosed HIV-infected individuals that entered into care in Aruba, the percentage receiving a resistance test at baseline increased from 26% in 2010 to 69% in 2015. Of all newly diagnosed patients tested for resistance, 33% (95% CI: 24-42%) was infected with a drug resistant HIV-variant. The prevalence of resistance to NNRTIs reached 45% (95% CI: 27-64%) in 2015, all based on the prevalence of mutation K103N. Patients infected with a K103N-strain were significantly more often MSM, diagnosed in more recent years and more often diagnosed during serologically confirmed recent infection compared to patients infected with wild-type virus. NGS did not demonstrate additional minority K103N-variants compared to routine resistance testing. In all 7 individuals in whom K103N was detected at baseline, NGS showed persistence of K103N at high frequencies despite the long duration of infection in some of them, suggesting high viral fitness of this particular strain. K103N-harboring strains were introduced into the therapy-naïve population via at least 6 independent transmissions. Transmission was frequently linked to individuals who were originating from and/or diagnosed with HIV in surrounding countries. One introduction subsequently spread widely into a large cluster of MSM (n=37), which expanded at a high rate between 2010 and 2012.

**Conclusions:** The prevalence of transmitted NNRTI-resistant HIV in Aruba has increased to alarming levels, compromising the WHO-recommended first-line regimen. As adequate surveillance as advocated by the WHO is limited, the Caribbean region could face an unidentified rise of NNRTI-resistant HIV. If strengthened surveillance would show that these NNRTI resistant viruses are more widespread in the region, a change of the current first-line NNRTI-based regimen to a regimen with a higher genetic barrier to resistance should be considered, despite its major implications for resources and logistics.

**Conflict of interest**

financial relationship(s): Travel grant from Gilead to gather data in Aruba

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**Abstract: 9**

**Transmission of HIV Drug Resistance**

**Extensive Intra-Host HIV Diversity Associated with Drug Resistance and Superinfection in U.S. National Surveillance Sequences**

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**Background:** A better understanding of the epidemiology of HIV-1 superinfection may shed light on factors that augment HIV transmission. We examined for evidence of superinfection within the U.S. National HIV Surveillance System by tracking shifts in genetic diversity and
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Virology of HIV Transmission

Transmitted HLA Pre-adapted Polymorphisms in the Gag Protein dictates viral evolution in the new host

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Background: HIV escapes adaptive cellular immunity by selecting mutations that are associated with the individual’s HLA-1 alleles. These mutations can be transmitted and they have been shown to determine the newly-infected individual’s disease progression but their impact on subsequent viral evolution in the new host is poorly understood.

Materials and Methods: In a group of 81 Zambian heterosexual transmission pairs, we...
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obtained the gag gene sequence at the time of transmission (donor and recipient; median=45.5 days post-infection) and two years after infection (recipient; median=765.5 days post-infection). The proportion of pre-adapted sites in the recipient virus was determined considering only polymorphisms present both in the donor and recipient at the time of transmission. IFN-g responses were evaluated for all sites according to each individual’s HLA alleles (N=20), using predicted peptides spanning each of these sites. The rate of reversion of pre-adapted polymorphisms as well as the proportion of newly-selected adapted polymorphisms was determined from the recipient sequence at two years post-infection.

Results: We found that a median of 25% of HLA-linked sites according to the recipient’s HLA alleles harbored a mutation associated with CTL escape in the transmitted virus. We confirmed that these polymorphisms impaired immune recognition since individuals exhibiting a higher proportion of pre-adapted sites (>50%) had a lower number and proportion of CTL IFN-g responses (p=0.004 for both, Mann-Whitney U test) when compared with individuals with a lower proportion of pre-adapted sites (<20%). Even when these pre-adapted epitopes were recognized and induced an immune response, it was of a lower magnitude when compared to that induced by non-adapted epitopes (p<0.009, Mann-Whitney U Test).

The rate of complete reversion of pre-adapted polymorphisms was low (3.5%) since out of 116 transmitted adapted polymorphisms, only 4 reverted to consensus. This rate is lower to that calculated for all transmitted polymorphisms in this same group of patients (5.2%, 101/1962) and significantly lower (p<0.0001, Mann-Whitney U Test) when we compare these two rates of reversion in a per patient basis. The proportion of adapted sites was significantly increased to a median of 40% during the two years of infection (p<0.0001, Wilcoxon matched-pairs signed rank test). Only one patient was found where the proportion of adapted sites was reduced (83% to 67%) while 31 remained the same and 49 showed an increase. Interestingly, the patients where the proportion of adapted sites was increased over the two-year follow-up had a significantly lower initial proportion of pre-adapted sites (median 22.2% vs. 40%; p=0.0014, Mann-Whitney U Test).

Conclusions: This study reveals that, even before an immune response is mounted, the degree of pre-adaptation of the transmitted variant determines the dynamics of viral evolution in the newly-infected individual. The fact that the level of viral adaptation rarely decreases and tends to increase when it was low in the transmitted variant is consistent with our previous finding on the relevance of viral preadaptation for HIV pathogenesis. This demonstrates that the advantage to the virus mediated by escape mutations persists during the first two years of infection and dictates viral evolution.

No conflict of interest

Abstract: 11

Virology of HIV Transmission

Deciphering the specificity of antibody profiles in patients that control HIV

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Background: Current vaccination strategies strive to induce HIV-specific antibodies (Abs), several types of which are of interest. Among them, neutralizing Abs (NAbs) are able to protect macaques against experimental infection but are difficult to induce by vaccination. The RV144 trial demonstrated a 31% reduction of infection without NAbs, correlated with the induction of anti-gp120 immunoglobulin (Ig) G3. Moreover, a study of HIC patients (HIV Controllers, undetectable viral load without therapy) showed that anti-gp41 IgG2s correlate with the lack of disease progression. These data suggest that the Fc domain and the heavy chain of the Ab

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(determining its isotype) play a crucial role in protection.

Methods: This study aims to characterize the isotypes and functional responses of Abs induced in sera of 37 HIC, 14 LTNP (Long-Term Non-Progressors, steady rate of CD4 T cells) and 21 ‘progressor’ patients. We hypothesize that LTNP and HIC have induced a particularly favorable Ab response. Therefore, we have analyzed the distribution of isotypes in the different cohorts. IgG subtypes were purified and analyzed for their functional activities.

Results: We found a variable induction of IgG subtypes: only few patients in each group induce anti-HIV IgG2 and 3. Interestingly, the anti-HIV IgG2 correlates with the total amount of IgG2 in sera of LTNP but not of HIC or ‘progressors’, suggesting a different regulation of IgG subtypes in these particular patients. Remarkably, the LTNP also display unexpectedly high neutralization of Transmitted/Founder viruses. This activity is observed for IgG1, 2 and IgG3.

Conclusions: These results show that polyclonal sera contain a wide variety of anti-HIV Ab isotypes with various inhibitory functions. The neutralizing profile of LTNP differs from HIV infected patients that either control replication or display high viral load. An in-depth characterization of the inhibitory activities will guide the design of new immunogens able to induce functionally relevant Abs by vaccination.

No conflict of interest

Abstract: 12

Biology of HIV Transmission

The role of gut homing receptor α4β7 in HIV pathogenesis and transmission- a prospective cohort study

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Background: The integrin α4β7 is critical for the homing of lymphocytes to the gut mucosa and gut associated lymphoid tissue. Several lines of evidence suggest important roles for α4β7 in SIV and HIV transmission and pathogenesis. Integrin α4β7 expression correlates with cellular activation and CCR5 levels in several compartments including the blood, gut, and female reproductive tract. Increased frequencies of α4β7 expressing CD4+ T cells within GALT at the time of infection appear to correlate with increased VL and rate of disease progression post SIV infection. The aim of this study was to assess the role of β7 Integrin in HIV acquisition and disease progressions in the CAPRISA 004 tenofovir gel cohort.

Methods: This was a matched case:control study at a 1:2 ratio (47 cases, 94 controls) with disease progression data and post-infection samples in 36/47 cases. PBMCs from a median of 110 days prior to infection were thawed, rested, and stained with a panel of antibodies designed to profile CD4+ T cells in terms of their memory, activation, and target cell properties. Matching was carried out on study arm, calendar month of enrollment, and age using a 5-year window; matched pairs were used as strata to adjust the analysis using conditional logistic regression, with additional potential confounders adjusted for in multivariate analyses.

Results: Our results show that higher integrin β7-Hi expression on blood CD4+ T cells is associated with higher HIV acquisition rates independent of age and HSV2 serostatus (p=0.035). The pre-infection β7Hi levels correlated significantly with increased VL, both peak (r=0.39, p=0.028) and median(r=0.37, p=0.039) and more rapid rate of CD4 loss (aHR=2.46, p=0.024) and a lower CD4:CD8 ratio (r=−0.30, p=0.03).

Conclusion: Our findings show that higher integrin β7-Hi expression on blood CD4+ T cells is associated with significantly higher HIV
acquisition rates, higher VL and faster disease progression in CAPRISA 004 cohort and demonstrate an important role for α4β7 in HIV pathogenesis and transmission.

No conflict of interest

**Abstract: 13**

**Biology of HIV Transmission**

**Gender Differences in Transmission of HIV-1 Viral Variants and Their Impact on Early Immune Activation**

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**Introduction:** Elucidating the early viral and host interactions in HIV-1 infection is critical to understanding transmission and subsequent disease progression. In a previous analysis of gag, pol, and nef in 135 transmission pairs, we identified a bias for transmission of consensus amino acid residues, which appears to be related to the transmission of viruses with greater overall fitness. However, females were infected with viruses that had significantly more non-consensus amino acids than males. We hypothesized that transmission of viruses with lower fitness to females may impact early immune activation.

**Material & Methods:** We evaluated inflammatory cytokine profiles in a group of males and females using a multiplexed Lumines assay and compared CD4+ and CD8+ T cell activation by multiparameter flow cytometry.

**Results:** We have found that early in infection (0 to 24 months), females exhibit lower VL and higher CD4+ T cell counts, as well as decreased levels of cellular immune activation in the CD8+ T cell compartment. We also found differences in early cytokine expression between genders, with females expressing lower levels of CCL2 and I-FABP. Using a Cox proportional hazards model, we found that in this cohort female gender was significantly linked to delayed disease progression even when accounting for confounding factors such as the presence of protective HLA alleles.

**Conclusions:** Our results on early immune activation of males and females contrast data gathered from the chronic stages of infection, in which females were shown to exhibit exacerbated immune activation. This suggests that the immunological response and inflammatory profile in females may differ between the acute and chronic stages of HIV-1 infection and may be related to the transmission of viruses with lower overall fitness. We are expanding on this finding by analyzing viral replicative capacity using infectious molecular clones (IMCs) in a group of male-to-female and female-to-male transmission pairs.

No conflict of interest

**Abstract: 14**

**Biomedical Approaches of HIV prevention of transmission**

**Impact of Targeted Pre-Exposure Prophylaxis Strategies for Men who Have Sex with Men in the United States**

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Introduction: Pre-Exposure Prophylaxis (PrEP) with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) has been demonstrated in randomized and observational studies to be effective in preventing HIV infection, including among men who have sex with men (MSM) - a population with the highest lifetime risk of HIV acquisition in the United States (US). We aimed to develop a novel agent-based simulation model to estimate the impact of different prevention strategies using FTC/TDF for PrEP (FTC/TDF_PrEP) among US MSM, including the number needed to treat (NNT) to prevent one HIV infection, the percent reduction in HIV prevalence (PRP), and the public health benefits (PHB).

Materials & Methods: CDC data were used as primary sources for epidemiological and behavioral assumptions, with 3.9% of US adult males being MSM. The model was calibrated to 2010-2013 estimates of HIV prevalence, by age and race, among US MSM. PrEP efficacy-adherence relationship was derived from the iPrEx-OLE study and with real world PrEP uptake, adherence and discontinuations from the PrEP DEMO project. Discontinuations rates were extrapolated forward using similar rates. Eligibility criteria were reassessed every 6 months. Outcomes, evaluated at 5 years, included: (1) NNT calculated as the person-time on FTC/TDF_PrEP divided by the number of infections avoided (among PrEP and non-PrEP users); (2) PRP from the 2015 HIV prevalence; and (3) PHB measured as the percentage of HIV infections that are avoided among non-PrEP users.

A risk-based indication for PrEP was established using the CDC HIV Risk Index (HIRI-MSM) (score ≥10 is considered an indication for PrEP). Each of the following FTC/TDF_PrEP prevention strategies was considered: PrEP for MSM with HIRI-MSM ≥10 (MSM-10+), PrEP for black MSM with HIRI-MSM ≥10 (BMSM-10+), PrEP for young (age <25) black MSM with HIRI-MSM ≥10 (YBMSM-10+), and PrEP for MSM with HIRI-MSM ≥20 (MSM-20+).

Results: The estimated 2015 HIV prevalence was 10.5%. The proportion of FTC/TDF_PrEP eligible HIV-negative MSM in the US under each preventive strategy would be: 50.5% with all MSM-10+: 21.6% with all MSM-20+, 5.1% with BMSM-10+, and 2.3% with YBMSM-10+. PrEP uptake and adherence among eligible MSM are predicted to be lowest in YBMSM-10+ (uptake: 66.2%; adherence: 63.1%). Average per person duration on FTC/TDF_PrEP ranged between 2.38 and 3.46 years. The NNT to prevent one new HIV infection is 70 if FTC/TDF_PrEP is targeted to all MSM-10+. The NNT is reduced to 33, 10, and 48 if targeted to BMSM-10+, YBMSM-10+, and MSM-20+, respectively. Focusing on making PrEP available to MSM-10+ would reduce HIV incidence by 50.0% and prevalence by 17.8% over 5 years, while the PRP with the other preventive strategies would be 4.0% for BMSM-10+, 2.9% for YBMSM-10+, and 9.4% with MSM-20+. PHB are estimated to be highest among YBMSM-10+ (37.8%), followed by MSM-20+ (26.4%), BMSM-10+ (25.3%), MSM-10+ (12.4%).

Conclusions: Offering FTC/TDF_PrEP to all eligible MSM yielded the highest reduction in US HIV prevalence but would require greatly expanded resources for delivery and cost of care. More focused preventive strategies with FTC/TDF_PrEP, based on sexual risk, age and/or race, substantially reduces the NNT and increases PHB.

Conflict of interest: financial relationship(s): Gilead, Jansen, Merck, Viiv (Adv. board, speaker bureaus, research grants)

Abstract: 15

Transmission of HIV Drug Resistance

Introducing dolutegravir into South Africa will eliminate resistance

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**Introduction:** Approximately 6.2 million people in South Africa are infected with HIV, ~50% are on treatment. The non-nucleoside reverse transcriptase inhibitor Efavirenz (EFV) has been used in first-line therapies since 2007, which has led to the emergence of drug-resistant strains with the mutation K103N. In South Africa, testing for drug resistance is uncommon. Integrase inhibitor Dolutegravir (DTG) is a new drug that has demonstrated the highest clinical barrier against drug resistance of any antiretroviral. If used as a second-line treatment, it can occasionally lead to the emergence of the mutation R263K. DTG is now being used in resource-rich countries, but not in South Africa. We model the impact of switching from EFV to DTG-based therapies, and/or introducing resistance testing. We predict the number of resistant infections that will be prevented between 2016 and 2030, tracking strains carrying the K103N or R263K mutation.

**Methods:** We use a transmission model parameterized using epidemiologic data from South Africa to reconstruct the history of treatment. The model includes both the evolution and transmission of resistance. We use orthogonal Latin Hypercube Sampling to conduct an uncertainty, and a multivariate sensitivity analysis based on response hypersurface modeling. Our input variables are treatment rates for different CD4-stages of infection, drug adherence/efficacy and the frequency of resistance testing.

**Results:** If current treatment conditions are maintained, annual incidence will decrease from 300,000 (median, IQR: 290,000-320,000) in 2016 to 170,000 (median, IQR: 140,000-210,000) in 2030. The total number of individuals with K103N due to TDR and acquired resistance will increase to 1,400,000 (median, IQR: 1,200,000-1,600,000). If resistance testing is introduced without DTG, 330,000 (median, IQR: 240,000-440,000) new infections due to TDR (K103N) will be prevented by 2030. The uncertainty in these predictions reflects a range in the frequency of testing from once every six months to three years. The more frequent the testing, the more TDR infections prevented. Furthermore, there will be significantly fewer (~200,000) individuals with K103N than if current treatment conditions are maintained. Switching from EFV to DTG-based therapies, and introducing testing, will prevent 860,000 (median, IQR: 650,000-1,100,000) new infections due to TDR, predominantly preventing strains of K103N. Notably, transmitted infections with the R263K mutation will arise, but will be less than 500 cases by 2030. The higher the adherence, the more effective DTG will be in preventing new infections with wild-type (WT) strains. The lower the adherence, the more effective DTG will be in preventing TDR and cases of acquired resistance.

If adherence is low, by 2030, there will be more individuals infected with WT strains than if current treatment conditions are maintained. However, ~1,200,000 cases of acquired resistance will have been prevented. Regardless of adherence, switching to DTG will prevent the greatest total number of new infections (WT + TDR): 950,000 (median, IQR: 820,000-1,100,000).

**Conclusions:** Introducing resistance testing into South Africa will be beneficial in terms of reducing TDR. Switching from EFV-based to DTG-based therapies will have an even greater impact on reducing TDR and will essentially prevent the development of acquired resistance.

*No conflict of interest*

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**Abstract:** 16

**Behavioral risk factors affecting HIV Transmission**

**HIV Care and Engagement: Demographics and Risk Factors associated with Retention and Viral Suppression in Chicago, IL**

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**Introduction:** People living with HIV/AIDS (PLWHA) and not engaged in HIV care pose a significant risk for transmission in an urban setting. In the U.S., more than 50% of PLWHA are not retained in care and approximately 75% of PLWHA are not virally suppressed. Identifying...
and understanding sociobehavioral risk factors associated with poor engagement in care are crucial for HIV retention and viral suppression.

**Material & Methods:** For PLWHA who attended at least one outpatient visit at our adult HIV care clinic, we collected patient demographics, visit history, behavioral risk factors, and laboratory results from January 2012 through May 2016. Patients accrued time until end of observation or transfer of care, while patients who died or moved out of our jurisdiction were excluded from the study. Using the Health Resources and Services Administration and HIV/AIDS Bureau measure, retention was defined as 2 attended visits with an HIV provider, ≥ 90 days apart within a 12-month period. Retention was classified into 3 groups: continuously retained (CR), intermittently retained (IR), or lost to follow-up (LTFU, i.e. no visit in the last 12-months). Viral suppression (VS) was achieved when HIV RNA was ≤ 200 copies/mL at a patient's most recent visit. Multivariate regression analyses were performed to assess the effect of sociodemographic variables on retention and VS. Outcomes retention and VS were independent of one another.

**Results:** 538 patients with 3859 provider visits (44.2 years, SD±16.5, 66.8% male) were observed over 4.5 years, predominately African-American/Black (79.8%) and of heterosexual risk (42.7%). Excluded from the study were those deceased (n=3) or moved (n=6) and as of May 2016, a total of 273 (51.6%) patients were CR, 102 (19.3%) were IR and 154 (29.1%) were LTFU. Patients that achieved VS were distributed among retention groups as followed: 56.8% were CR, 20.7% were IR and 22.5% were LTFU. Our analyses found that females were 2.5 times more likely to be CR compared to LTFU than males (p=0.01, 95% CI 1.26, 5.51), while patients with household sizes ≥2 were 4.9 times more likely to be retained compared to LTFU than living alone (p=0.01, 95% CI 1.41, 17.47). Older age was negatively associated with retention (p=0.007, 95% CI -0.03, -0.01), yet positively associated with VS (p<0.001, 95% CI 0.01, 0.05). We also found that those perinatally HIV-infected were 87.4% less likely to be VS compared to MSM (p=0.02, 95% CI 0.02, 0.67). Lastly, patients with a higher CD4 count were more likely to be retained (p=0.0001, 95% CI 1.001, 1.002), as well as be virally suppressed (p<0.001, 95% CI 1.003, 1.005).

**Conclusions:** Risk factors for LTFU or lack of VS included male gender, living alone, perinatal infection, age, and low CD4 count. Tailoring interventions and resources to improve engagement in care may be targeted for these vulnerable groups of PLWHA. In a future project, we plan to use these data to develop an algorithm that will identify and predict the likelihood that patients may fail to engage in HIV care at our clinic to inform retention-in-care interventions.

**No conflict of interest**

**Abstract: 17**

**Behavioral risk factors affecting HIV Transmission**

**Patterns of Anal Sex Practices and its contribution to heterosexually acquired HIV infections among high-risk women in the US**

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**No conflict of interest**

**Abstract: 17**

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**Patterns of Anal Sex Practices and its contribution to heterosexually acquired HIV infections among high-risk women in the US**

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**No conflict of interest**

**Background:** HIV risk is greater during unprotected receptive anal intercourse (URAI) than vaginal intercourse (UVI). RAI practice and its role in the US heterosexual HIV epidemic are poorly understood. We aimed to 1) describe patterns of RAI and to 2) estimate the contribution of URAI to HIV infections heterosexually acquired by high-risk women each year.
Abstract: Method: Data from the 2010/2013 National HIV Behavioral Surveillance (respondent-driven samples of low-income women living in 20 high-HIV prevalence cities, N=39-325) were used to derive model parameters for each city, including past-year RAI (RAI practiced in the past year) and RAI frequency (RAI at last sex among those reporting past-year RAI) by key demographic characteristics and to compare sexual behaviour of women reporting/not reporting past-year RAI. City-level estimates were pooled to produce overall RAI estimates. These and HIV incidence estimates from a similar population (HPTN-064) served to calibrate a risk equation model to predict the overall fraction of HIV infections heterosexually acquired due to URAI (from 10000 parameter fits).

Results: Overall past-year RAI (31% 95%CI:29-34%; city-range:5-64%) was high across cities, even among 18-19 year-olds (city-range:6-57%) and ~2 times as high in women who exchanged sex for money or drugs. RAI frequencies (overall 35% 95%CI:32-37%) were higher in cities with higher past-year RAI. Overall 11% (95%CI:9-12%) of all unprotected sex acts among the whole study sample were URAI. Women reporting past-year RAI had ~3 times as many annual sexual partners (city-range means: 4.0-26 vs 2.2-6.4) and used condoms less often at last RVI than those who did not. Overall 40% (10th-90th percentiles: 15-64%) of heterosexual HIV infections among high-risk women may be due to UAI. Aside from the increase in HIV risk per URAI vs UVI, the fraction of condomless acts that were URAI was also influential, highlighting data needs.

Conclusions: Many high-risk women practice RAI in the US and have other higher-risk behaviours. URAI may contribute more substantially to heterosexual HIV incidence in the US than originally assumed which has important implications for prevention.

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Behavioral risk factors affecting HIV Transmission

Circumcision for HIV prevention: perceptions about post-circumcision sexual behaviours in rural Uganda

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Introduction: Medical male circumcision (MMC) is currently recognized as an additional important HIV preventive intervention to reduce the risk of heterosexually acquired HIV infection in men. However, sexual behaviours after medical circumcision can potentially reduce the expected benefits of the practice. This study explored the perceptions about medical male circumcision and sexual behaviours of adults in Kayunga district, Uganda.

Methods: A cross-sectional study was carried out among 393 respondents using a semi structured questionnaire. In addition, four focus group discussions among different groups of married men, married women, single men and single women were conducted. Quantitative data was analysed using STATA 12 statistical software. Univariate, bivariate and multivariate analyses were carried out. Qualitative data was analysed thematically and presented using quotes.

Results: Majority 383 (97.5%) of respondents had heard about MMC and more than half 206 (53.8%) believed that MMC could prevent a man from acquiring HIV. A total of 39 (10.2%) thought that MMC provided 100% protection against HIV acquisition while 291 (76.0%) thought it did not. Regarding the recommended time between circumcision and resumption of sexual intercourse, majority 226 (59.0%) of respondents mentioned between 6-12 weeks, whereas 127 (33.2%) said between 1-5 weeks and the rest 30 (7.8%) more than 13 weeks. This study established various perceptions about medical male circumcision and sexual behaviours. Among

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the respondents, majority 247 (64.5%) did not perceive circumcision as a practice that can lead men to have multiple sexual partners. Males were 3 times more likely to think that circumcision would lead to having multiple sexual partners than females (AOR=2.99, CI: 1.93-4.61). Only 89 (23.2%) believed that circumcision would compromise the use of condoms to prevent against infection with HIV. Respondents who had education above primary were less likely to think that circumcision would compromise the use of condoms (AOR=0.49, CI: 0.31-0.79). Focus group discussions revealed concerns about promoting MMC as a measure to reduce HIV infection and the sense of protection provided by the procedure which respondents thought would lead to indulgence in risky sexual behaviours. The perception that circumcised youths were less likely to abstain from sexual intercourse was less held among those with education above primary (AOR=0.58, CI: 0.37-0.91) and those older than 30 years (AOR=0.59, CI: 0.38-0.92).

Conclusion: There were gaps in knowledge and negative perceptions about MMC in the study community. Measures are needed to avert the negative perceptions by equipping communities with sufficient, accurate and consistent information about medical male circumcision and sexual behaviour.

No conflict of interest

Abstract: 19

Modeling of HIV Transmission

Characterization of the early HIV infection in mucosal tissue explants

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Introduction: Several routes of HIV-1 infection at the mucosa were proposed; however, the very early events leading to infection are still controversial. Ex-vivo studies of HIV-1 infection of mucosal explants showed that CD4+ T cells are the major viral target, when analyzed after 7-14 days, thus, when multiple rounds of cell-to-cell transmission events had occurred. Conversely, recent data demonstrated a rapid redistribution of dendritic cells (DCs) at the epithelial layer after HIV incubation. Moreover, DCs described to be highly HIV restricted- were found to be HIV susceptible when co-cultured with autologous T cells. We therefore wanted to identify the very early cells infected by HIV in the context of mucosa.

Material & Methods: Method 1: monocyte derived DCs and their corresponding PHA-activated autologous T cells were co-cultured with infected T cells from a heterologous donor at a DC/T cell ratio of 1:4. Infected cells identified by p24 staining were phenotypically characterized at day 1, 2 and 3 by FACS. Method 2: cells isolated from cervico-vaginal tissues were infected with HIV and the early infection events characterized. Method 3: Cells from colonic tissue explants were phenotypically characterized via confocal microscopy and infection events followed.

Results: We found that DCs were the first HIV positive cells detected only after 1 day of DC/T cells co-culture. In addition, DCs were the early HIV target despite the presence CD4 T cells in the infection model with cervico-vaginal tissues. Similarly, CD11c+ DCs of the colonic mucosa migrated to the epithelial surface in the presence of an intact epithelium. Extensive phenotyping of the infected cells is ongoing.

Conclusions: These results indicate that DCs are strategic in the early steps of infection and dissemination in mucosal tissues following sexual transmission. The development of an HIV
Abstract

A prophylactic vaccine should include DCs as a relevant target taking into account their role as a virus vehicle and as mediators of efficient local antibody responses.

No conflict of interest

Abstract: 20

Virology of HIV Transmission

Near Full Length Genome Amplification and Sequencing of Acute HIV-1 Infections in Virologically-linked Heterosexual Transmissions in a Rwandan Cohort

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Background: Determination of transmitted founder virus (T/F) genomic sequences is key to understanding the earliest immune responses during HIV infection. In previous studies of HIV Env sequences, in the Projet San Francisco (PSF) Rwandan acute HIV infection cohort we showed that only one genetic variant from the transmitting partner established infection in a majority (85-90%) of transmissions. Here, we aimed to define the complete genomic sequence of the T/F virus in individuals with acute HIV infection.

Materials & Methods: We collected plasma samples from partners with acute HIV infection in the PSF cohort, a median of 17 days post-estimated date of infection. We used high-fidelity polymerase amplification on viral cDNA to obtain near full-length (NFL) single-genome amplification, PacBio SMRT technology for genome sequencing, and Geneious software for phylogenetic analyses.

Results: We sequenced and amplified NFLG from 22 patients with acute HIV (median 11 amplicons/patient). Phylogenetic analyses showed that 18% (4/22) of HIV infections were established by 2 or more T/F viruses. Moreover, one C clade variant as well as 3 A/C and 1 C/D inter-subtype recombinants (18% recombinant) were identified in this A1 subtype dominant (77%) cohort. Pol and Env sequencing had previously identified only two of the A/C recombinants. For each patient the recombination pattern was unique.

Conclusions: We found a relatively high rate of inter-subtype recombination in these patient samples from the PSF acute heterosexual HIV transmission cohort. Because of the unique breakpoints for each HIV recombinant, full-length genome amplification and sequencing are essential to identify and fully characterize these HIV variants. This approach will allow us to build a cohort specific T/F HIV sequence database in order to characterize early immune responses. It further provides critical information for studying virus-host interactions and early viral adaptation to host immune responses that are relevant to HIV-1 vaccine development.

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No conflict of interest

Abstract: 21

Behavioral risk factors affecting HIV Transmission

Depression, self-efficacy, and sexual behaviour among men who have sex with men

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Introduction: The role of depression as a determinant of HIV/STI risk among men who have sex with men is poorly understood. Although there is evidence of a link between depressive symptoms and sexual behaviour, the mechanisms by which it operates, and implications for intervention, are uncertain. The association may be due to the tendency of individuals with depression to experience lowered self-efficacy for sexual safety (lowered confidence in one’s ability to ensure condom-use).

Material & Methods: The Attitudes to a nd Understanding of Risk of Acquisition of HIV (AURAH) is a cross-sectional study of HIV-negative individuals attending UK GUM services (2013-2014). Associations between (i) depressive symptoms (score of ≥10 on PHQ-9) and sexual behaviour, (ii) depressive symptoms and self-efficacy, (iii) self-efficacy and sexual behaviour, and the effect of adjustment for self-efficacy on the association between depressive symptoms and sexual behaviour, were investigated among 1340 MSM reporting recent sex using modified Poisson regression, adjusted for age, UK-born, sexual identity, education, relationship, and region. Sexual behaviour included measures of condomless sex (CLS) partners in the past three months: (i) any, (ii) ≥2, (iii) unknown/HIV+ status, (iv) receptive unknown status, and the following additional measures (past year): (v) STI diagnosis and (vi) PEP use. We defined strong agreement with the statement ‘I feel confident that, if I want to, I can make sure a condom is used with any partner, in any situation’ as indicating high self-efficacy for sexual safety. Difficulty negotiating condom use was defined as agreement with the statement ‘I find it difficult to discuss condom use with any new sexual partner’.

Results: The prevalence of depressive symptoms was 12.4%. Prevalence of sexual behaviour was 63.7%, 32.1%, 35.4%, 14.0%, 31.6%, and 15.5% for measures (i)-(vi) respectively. Prevalence of high self-efficacy was 67.2%, and 10.6% for difficulty negotiating condom-use. Depressive symptoms were associated with CLS partners (any [adjusted prevalence ratio, aPR 1.18 95%CI 1.06, 1.30; p=0.002]; ≥2 [aPR 1.42 95%CI 1.17, 1.74; p=0.001]; unknown/HIV+ [aPR 1.43 95%CI 1.20, 1.71; p<0.001]; receptive unknown [aPR 1.60 95%CI 1.14, 2.24; p=0.006]), STI [aPR 1.46 95%CI 1.19, 1.79; p<0.001], and PEP [aPR 1.83 95%CI 1.33, 2.50; p<0.001]. Depressive symptoms were associated with lowered self-efficacy [aPR 0.82 95%CI 0.71, 0.94; p=0.006], and difficulty negotiating condom-use [aPR 1.77 95%CI 1.18, 2.63; p=0.005]. High self-efficacy was associated with lower prevalence of CLS partners, STI and PEP. Difficulty negotiating condom-use was associated with higher prevalence of CLS partners. After adjusting additionally for high self-efficacy, associations between depressive symptoms and CLS partners (including STI) were attenuated (any [aPR 1.12 95%CI 1.01, 1.24; p=0.027]; ≥2 [aPR 1.31 95%CI 1.08, 1.59; p=0.005]; unknown/HIV+ [aPR 1.32 95%CI 1.11, 1.57; p=0.002]; receptive unknown [aPR 1.47 95%CI 1.05, 2.07; p=0.025]; STI [aPR 1.42 95%CI 1.16, 1.74; p=0.001]). Adjusting for difficulty negotiating condom-use, associations were slightly attenuated with CLS partners.

Conclusions: Depressive symptoms were strongly associated with CLS. Lowered self-efficacy/difficulty negotiating condom-use may be a mechanism through which depression leads to CLS. Management of depression alongside interventions surrounding self-efficacy/negotiation of condom-use may play an important role in HIV/STI prevention.
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Biology of HIV Transmission

Distribution of CCR5+ CD4+ cells in inner and outer foreskin

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Background: Male circumcision reduces heterosexual HIV acquisition by as much as 60% and is currently encouraged by the World Health Organization as a prevention measure. The mechanism by which circumcision protects against infection is still poorly understood and requires further study. We hypothesize that the distribution of target cells in tissue is skewed towards vulnerability in uncircumcised men.

Material & Methods: Inner and outer foreskin biopsies from 24 young males (18-24) were cryo-sectioned and stained for HIV-1 receptors CD4 and CCR5. Deconvolution fluorescence micrographs were manually analyzed for the presence of cells positive for one or both markers in the epithelium and sub-basal tissue, and for epithelial tissue area.

Results: We find that the majority of CD4+ cells are also CCR5+. However, when we consider the two layers separately, we find that in the epithelium, the proportion of CD4+ cells that are CCR5+ is noticeably higher than in the sub-basal connective tissue. We observe this trend for both inner and outer foreskin. When consolidating data from all images for each donor we can calculate the inner-to-outer foreskin ratio of the preponderance of CCR5+ cells among CD4+ cells. We observe that the whole-tissue and sub-basal analyses yield a moderate bias towards ratios less than 1. This indicates that the preponderance of CCR5+ cells among CD4+ cells is somewhat lower in inner foreskin than in outer foreskin. However, considering the epithelium, the bias is slightly towards values greater than 1, indicating a higher preponderance of target cells in the inner foreskin.

Conclusions: Our data supports the hypothesis that, in the epithelial layers, CD4+ cells are more likely to express the necessary HIV co-receptor CCR5 in inner foreskin than in outer foreskin.

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Transmission of HIV Drug Resistance

Transmission of Diverse Minority HIV RT Variants with Multiple Drug Resistance Mutations

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Background: We’ve recently reported on multiple drug-resistant variants at minority levels in transmitted HIV populations of homogeneous env sequences during early acute viremia. An understanding of the implications of HIV subpopulations with diverse subgenomic regions in the context of HIV transmission is important for the design of biomedical interventions. Here, we applied a novel HIV particle immunocapture algorithm that segregated virions by host cell source for a deeper understanding of the diversity of expressed variants during early infection as a reflection of the infecting swarm.

Materials and Methods: Plasma from 32 persons from surveillance and biomedical intervention studies documented to have durations of infection of between 1-6 weeks, and for two acute infections related cases with established infections, were first genotyped by deep sequencing to characterize HIV variants. The plasma specimens were then applied to a series of ten magnetic immunocaptures to segregate virions by the cluster of differentiation (CD) proteins that were incorporated into the particle envelopes during the budding process. This capture algorithm allows for enrichment of particles that originated from myeloid and lymphoid cell types as well as from different developmental stages known to be
Abstract

Virology of HIV Transmission

HIV-1 Subtype C Transmitted/Founder Variants Do Not Downregulate HLA-I, CD4 or CD62L Differently Than Non-Transmitted Donor Variants

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HIV-1 is subject to a severe genetic bottleneck upon transmission to a new individual such that in ~80% of heterosexual transmission events, one variant is transmitted. We have previously reported a bias during transmission for more consensus-like HIV-1 variants—particularly evident in sequences from Nef functional domains responsible for CD4 and HLA class I downregulation. Here, we investigated whether downregulation by Nef differed in transmitted/ founder (TF) and source quasispecies non-TF (NT) infectious molecular clones (IMC).

We tested 32 IMC from 5 transmission pairs, and two lab adapted strains, NL4.3 and MJ4. We developed a flow cytometry panel to measure the extent of CD4, HLA-I (A2 & B7 alleles) and CD62L downregulation on infected CD4+ T-cells in vitro. HLA-I downregulation ranged from 1.1 to 7.3-fold (mean 2.8-fold) by median fluorescence intensity (MFI) in infected T-cells. Overall, TF variants were not significantly different from the median of their donor IMCs (p=0.31, Wilcoxon). CD62L downregulation ranged from 4.7 to 42-fold (mean 22-fold) by MFI, and again no difference was observed between TF and NT variants (p=0.99). CD4 downregulation ranged from 30 to 69-fold (mean 55-fold) by MFI, and was similar for TF and NT variants (p=0.99). The pairwise distance to the amino acid subtype C consensus correlated with CD62L downregulation (r=.47, p=.002, Spearman)

Conclusions The evidence in transmitting viral populations of substantial RT diversity while maintaining homogeneous envelopes supports the env sequence being a major restriction factor in transmission. Furthermore, this also suggests HIV generates a tremendous amount of recombinant variants outside of env in the source prior to transmission. Further study is needed to determine if these highly diverse populations play a role in circumventing biomedical interventions even if they do not persist after seroconversion.

No conflict of interest

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but not HLA or CD4 downregulation (p=0.66; 0.26; Spearman). In addition, consensus Nef71R containing variants in these transmission pairs did not differ in HLA downregulation phenotype compared to Nef71K polymorphic variants (p=0.90, Mann-Whitney).

In conclusion, the ability of Nef to downregulate key cell surface immunoregulatory molecules does not appear to be a major differentiating factor for TF variants from these subtype C transmission pairs under study. The phenotypic correlate of the consensus TF signature is still yet to be determined.

No conflict of interest

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Biology of HIV Transmission

‘Transmission’ signatures are also ‘Infectivity’ signatures enabling HIV to sustain rebounding infections

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Introduction: Developing an effective HIV vaccine is one of the most important health challenges worldwide. Traditional strategies of HIV vaccine design have been thwarted by substantial genomic divergence among circulating variants rendering them ineffective at inducing enough cross-reactive immunity. Here, I will present a novel approach deviating from traditional strategies aiming to encompass viral diversity to instead capture sites of extreme conservation.

Material & Methods: The alternate approach identifies sites critical to HIV survival to exploit as potential viral vulnerabilities in vaccine design. Previously, we discovered six gp120 signatures conserved in HIV, SHIV, and SIV transmitted/founder (T/F) viruses. Now, I extend the analysis across a broader phylogenetic and sequence scale by scanning for signatures in all primate and non-primate lentiviruses sequenced to date.

Results: The study finds that the ‘Transmission’ signatures are also ‘Infectivity’ signatures enabling HIV not only to initiate but also to sustain rebounding infections. These sites are under strong selection and critical to survival of T/F, rebounding/founder, and circulating lentiviruses. The evolutionary history of the signatures recapitulates all documented cross-species transmissions leading to HIV-1 and HIV-2 and suggests origins of the precursor of HIV-1 and of SIVcpz.Pts. This work also suggests mechanisms driving selection at the signature sites. Glycosylation at one site consistently enhances infectivity of lentiviruses as a venue for immune escape exclusive to primates. Another site seems to be involved in tropism by modulating a switch of coreceptor usage.

Conclusions: This work is the first study to examine transmission and infectivity signatures at such a large genomic and phylogenetic scale. The infectivity sites represent possible biological susceptibilities common to productive infections, which if targeted in combination with antiretroviral therapy could provide a means to combat the HIV epidemic.

No conflict of interest

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Biology of HIV Transmission

Fc-gamma Receptor Affinity as a Host Factor for HIV Transmission

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Introduction: Heterosexual HIV transmission is modulated by host and viral factors. Previous HIV vaccine trials have suggested that the Fc-gamma receptor (FcγR) is one such host factor. The human FcγRIIa and FcγRIIIa alleles are polymorphic, with SNPs resulting in different affinities for IgG antibodies. Changes in receptor affinity affect immune cell effector function and even HIV disease progression. This study aims to assess the potential role of FcγRs on HIV acquisition in a heterosexual transmission cohort.

Methods: The 378 participants in this study, from the Zambia-Emory HIV Research Project (ZEHRP) study cohort, were categorized into: uninfected males (89), uninfected females (84), infected males (105), and infected females (100). Each was genotyped at both FcγRIIa and FcγRIIIa loci, using genomic DNA and a real-time PCR method, to define homozygous high affinity (Hhi), heterozygous (Het), or homozygous low affinity (Hlo) genotypes at each locus.

Results: In this subtype C population, no significant difference in allele frequency for either receptor was observed between infected and uninfected groups (p=0.97; 0.59). Men had a higher frequency of the Hhi genotype, and women a higher frequency of the Hlo genotype, regardless of infection status, however this finding was not statistically significant (p=0.07). The distribution of FcγRIIa alleles was 21% Hhi/49% Het/30% Hlo, while the FcγRIIIa allelic distribution was heavily skewed towards low affinity alleles with an 8%/37%/55% distribution.

Conclusions: The genotypic distribution of FcγR alleles in the Zambian population was previously unknown, as is the role of FcγR affinities in HIV acquisition. Although no significant difference was observed based on HIV infection status in this small sample, further analyses on the impact of FcγR genotypes on the frequency and time to transmission, as well as disease progression, in the context of donor viral load, genital inflammation, HLA alleles, and replicative capacity of the transmitted virus are warranted.

No conflict of interest

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Virology of HIV Transmission

Inter-Subtype Recombinant HIV-1 identified by full-length Transmitted/Founder virus sequencing across three African acute transmission cohorts


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Background: The extreme genetic variation observed in HIV-1 is a major challenge for vaccine design, treatment and control of disease progression. Recombinant forms (RFs) of HIV-1 with unique recombinant breakpoints can potentially affect viral epidemiology, as well as susceptibility to host humoral and cellular immune responses. As part of the IAVI Vaccine Immunology Science and Technology for Africa (VISTA) training program for young African investigators, we have initiated a study of viral diversity using medium throughput near full-length single HIV-1 genome PCR and sequencing of virus populations in acute infection. These analyses are designed to provide a large database of Transmitted/Founder (T/F) sequences to assist in vaccine design and studies of host immune control of disease progression.

Material & Methods: Acute infection samples from the Kilifi, Kenya MSM cohort, the Project San Francisco, Rwanda epidemiologically linked heterosexual transmission cohort and the
Uganda heterosexual transmission cohort, representing 3 IAVI clinical centers, were analyzed. Near full-length (>9000bp) single genomes (NFLG) were amplified from plasma viral RNA. In order to obtain full-length viral sequences we used a multiplexed, highly-accurate, DNA sequencing approach based on the PacBio Sequencing platform. This allowed the definition of the T/F virus sequence(s) and unique recombinant forms (URFs).

**Result:** A total of 592 NFLG amplicons were obtained from a total of 58 individuals from the 3 sites. Phylogenetic analyses of near full-length genome sequences allowed the definition of the presumptive T/F virus genome in a majority of cases. Although single gene (pol) sequencing had suggested a low frequency of recombinant forms in these cohorts, analysis of the NFLG sequences showed that 37% of the acutely infecting viruses represented URFs in the Kilifi MSM cohort (A1/D, A1/C, A1/B, A1/A2/D); 18% inter-subtype URFs (A/C and C/D) were identified in the Rwanda cohort, and an unexpectedly high frequency of 70% (A/D and A/C/D) URFs were identified in the Uganda acute heterosexual transmission cohort.

**Conclusion:** The VISTA training program provides a unique opportunity for young African investigators to gain experience in molecular virology while generating an insight into the molecular epidemiology of viruses transmitted in their respective cohorts. The results of these studies have demonstrated the importance of defining NFLG sequences in fully understanding the nature of the T/F virus(es) and the prevalence of URFs in these East African communities.

**No conflict of interest**

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**Abstract: 28**

**Behavioral risk factors affecting HIV Transmission**

**They are likely to be there:** Family testing approach to facilitate achievement of 90:90:90 strategy among Children in Kenya

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**Background** In Kenya, less than half of all children 18 months to 14 years old with a HIV-positive parent have ever been tested for HIV. Strategies to identify and test children at increased risk for HIV are critical. This study examined the impact of a family-centered approach to reach children (0-14 years) with HIV testing.

**Methods** We conducted a retrospective review of clinical records among a convenience sample of 60 high-volume clinics in Kisumu, Homabay and Migori counties. We reviewed the records of adult index patients who were enrolled in family-centered HIV care between May–July 2015 and followed family outcomes through October 2015. Family member testing status, results, enrollment in care and ART initiation for those positive were abstracted; chi-square test was used to compare the positivity proportion differences among children to 1) prior studies¹,² that used the family approach in the same region and 2) outpatient and inpatient testing data performed in the same region from July–September 2015.

**Findings** Review of 1,937 adult patient charts led to the identification of 3,033 eligible children for...
testing. There were 1,869 (62%) children tested, among which 100 (5.4%) were HIV-positive, of whom 87 (87%) were successfully linked to care and 73 (84%) had initiated ART by October 2015. Compared to prior evaluations, a declining trend in HIV positivity among children was found with the family-centered approach: the proportion of children testing positive went from 18% in 2009 to 7.4% in 2012 to 5.4% in 2015 (p<0.001). Positive proportions among children reached through the family approach were higher than inpatient 24/1,636 (1.5%; p<0.001) and outpatient 309/46,002 (<1%; p<0.001) testing proportions.

Conclusion

The family approach leads to high proportion of HIV positive children identified, linked to care, and initiated on ART. Although HIV positive proportions among children were lower than observed in previous family approach studies and appear to be declining, it continues to have a higher yield than program-wide inpatient and outpatient testing. The family-testing approach offers an important entry point for identification of children at risk of HIV and the opportunity for targeted follow-up through the HIV care cascade.

No conflict of interest

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Biology of HIV Transmission

Transcytosis as a Mechanism of HIV Entry into Columnar Epithelial Explants of the Female Reproductive Tract

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During male-to-female transmission, HIV needs to cross the mucosal epithelium of the female reproductive tract to gain access to underlying target cells. Previously, we illustrated that HIV is able to penetrate intact columnar and squamous genital epithelia in both ex vivo and in vivo systems. However, we were only able to illustrate that virus enters the squamous epithelium in a diffusion-based mechanism. By utilizing a similar series of approaches, we are now able to illustrate a possible mechanism for virus penetration into the endocervical simple columnar epithelium. Although previous studies have implicated translocation as a penetration mechanism in transwell culture systems, we examine this mechanism with human explant cultures. Utilizing this ex vivo system, we are able to illustrate transcytosis as another possible mechanism of HIV penetrating past the endocervical columnar barrier to reach underlying immune cells. Human cervical explants were exposed to V-ATPase inhibitor Bafilomycin A1 (BafA1), receptor-mediated endocytosis inhibitor Chlorpromazine (CPZ), and cell-free PA-GFP BaL HIV. Control samples were incubated with virus in the absence of BafA1 and CPZ treatment. Following, samples were removed, snap frozen, sectioned, stained and imaged accordingly through deconvolution fluorescent microscopy. Comparison of the image z-stacks pre and post-photoactivation revealed viral signal, accounting for background. In our human ex vivo control samples, PA-GFP BaL HIV was found to enter the simple columnar epithelium of the endocervix to depths up to 50 microns. We also confirmed that virions penetrated to depths were target cells reside. In contrast, both BafA1 and CPZ treated samples had a smaller number of penetrating virions. Likewise, deep penetrators past the simple columnar barrier, into the lamina propria, were rarely observed. The majority of virions observed were noted either within the simple columnar barrier itself (BafA1-treated) or on the luminal surface of the simple columnar barrier (CPZ-treated). Overall, our control samples confirmed our previous work that PA-GFP BaL HIV-1 is able to penetrate the intact columnar epithelium, to depths of 50 microns, thereby gaining access to underlying target cells. In contrast, virions in BafA1 and CPZ treated samples were less likely to be observed past the columnar barrier, within the lamina propria. In all treated samples, a trend in the decrease of the number of penetrating virions was also noted, with CPZ treated samples having the lowest amount of penetrating virions. Collectively, this data suggests a transcytosis-based mechanism for HIV penetration into the endocervical columnar barrier.
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Biomedical Approaches of HIV prevention of transmission


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Background: Over the last few years, the availability of FTC/TDF for pre-exposure prophylaxis, in combination with other strategies to reduce the risk of sexually acquired HIV-1 in adults at high risk, has altered the HIV prevention landscape. Previous analysis has shown gender (Flash, HIV Drug 2014) and racial (Bush ASM 2016) differences among individuals started on FTC/TDF for PrEP. Here we describe characteristics and differences in utilization by payor type and provider specialty.

Materials & Methods: National electronic patient level data was collected from 82% of all US retail pharmacies that dispensed FTC/TDF between January 1, 2012 and December 31, 2015. A previously described algorithm identified use of FTC/TDF for PrEP. De-identified patient and provider demographics, prescription refill data and medical claims were analyzed through categorical methods. Data was analyzed by payor type and provider specialty.

Results: A total of 79,684 unique individuals (23% female) were started on FTC/TDF for PrEP by over 120 different medical subspecialties. Four specialties, Family Practice (FP), Internal Medicine (IM), Infectious Diseases (ID) and Emergency Medicine (EM) accounted for 84% of all starts. Among males FP (35%) and IM (28%) were the 2 primary prescribers. For females, EM (25%) and FP (23%) were the primary prescribers. Starts in men were covered by commercial plans (62%) and Medicaid (16%). For women the largest payor was Medicaid (44%) with commercial plans accounting for (33%) of starts.

Conclusion: Our analysis shows gender differences in which medical specialties prescribe, and the type of plans that cover, FTC/TDF for PrEP. Higher levels of commercial plan coverage for males, and greater starts among women by EM providers, have potential implications for linkage to prevention services and the implementation of FTC/TDF for PrEP clinical management. Additionally, these finding highlight the need for different strategies for prescriber education and access to prevention care for men and women.

Conflict of interest financial relationship(s): All authors are employees and shareholders of Gilead Sciences

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Transmission of HIV Drug Resistance

Trends in transmitted antiretroviral drug resistance in an urban HIV clinic in North Carolina

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BACKGROUND: The 2012 World Health Organization (WHO) report estimates that prevalence of transmitted drug resistance mutations (TDRMs) in HIV-infected treatment-naive patients in high-income countries (United States, some European countries, Australia, Japan) is 10-17%. We sought to assess the trend of TDRMs in a single practice in Charlotte, NC, USA, 2008-2014.
MATERIALS & METHODS: The primary endpoint was the prevalence of TDRMs 2008-2014. Antiretroviral (ARV) drug susceptibility was retrospectively analyzed in treatment-naïve patients 2008-2014. Resistance was defined on the basis of the International AIDS Society 2015 definition. Secondary endpoints included TDRM rates in recently diagnosed patients (HIV diagnosis in the last 12 months), predictors of persistence with care (12 months of follow-up data available) in patients who were initiated on ARVs 2008-2014, and virologic success (HIV-1 RNA <50 copies/mL after 12 months of therapy). Descriptive statistics, Pearson’s chi-square analysis, Fisher’s exact, and logistic regression methods were used to analyze results.

RESULTS: Among 333 treatment-naïve patients who entered care 2008-2014 (75% male, 88% African American, median CD4 count 312 cells/mm³), 48 (14%) had >1 TDRM. Year-to-year comparisons indicated a 0% TDRM rate in 2008, 12% in 2009, 8% in 2010, 16% in 2011, 10% in 2012, 24% in 2013, and 24% in 2014 (p=0.033). Among 243 recently diagnosed patients, TDRM rates were 0% in 2008, 13% in 2009, 10% in 2010, 20% in 2011, 11% in 2012, 20% in 2013, and 29% in 2014 (p=0.12). NNRTI resistance was most common (38/48; 79%), followed by NRTI (5/48; 10%) and PI (2/48; 4%). Dual class resistance was noted in 3 (6%) patients. Of the 313 patients initiated on HAART 2008-2014, 243 (78%) demonstrated persistence in care and 201 (64%) achieved virologic success. Factors associated with persistence in care included recent HIV diagnosis (p=0.012), age (p=0.005), and initiation of HAART (p<0.001). Factors associated with achieving HIV-1 RNA <50 copies/mL included a recent HIV diagnosis (p=0.002), age (p=0.039), and female gender (p=0.026).

CONCLUSIONS: The prevalence of TDRMs in our clinic through 2012 resembled the 2012 WHO report, but increased significantly in 2013 and 2014. Clinical outcomes such as persistence in care and virologic success rates are suboptimal, and efforts must be focused on improving these outcomes in urban HIV clinic settings.

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MVC 12.5-10971ng/g, RAL 128-896780ng/g and LPV 1654-32699ng/g (no previous data available for comparisons). AUC infectivity was lower at day 7 (mean: 513±1231) and 28 (mean: 427±547) than at day 90 (mean: 513±877) in the MVC arm (p=0.0002 and p=0.02, respectively). No significant differences were observed in LPV/r and RAL arms. We found no significant correlations between plasma or RT concentrations and infectivity. In patients receiving MVC we observed an increase in the expression of CCR5 in CD4 (4.7% vs 15%, p=0.002) and CD8 (6.3% vs 16.1%, p=0.004) T-cells in blood between baseline and day 28.

Conclusions: Individuals receiving MVC for PEP showed plasma and RT concentrations within expected range, a reduction of viral replication in ex-vivo RT explants and an increase in markers of chemotaxis. Conversely, neither RAL nor LPV/r prevented ex-vivo infection of RT. This data would be useful for selecting prophylaxis strategies based on ARV therapy.

No conflict of interest

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Mother to Child Transmission

Mother-to-Child HIV Transmission and its Predictors among HIV-Exposed Infants under Prevention of mother to Child Transmission Program in Southwest Ethiopia

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Background: Ethiopia is among countries most affected by HIV/AIDS pandemic. HIV prevalence among pregnant women is estimated at 2.4% and approximately 38,401 pregnant women are living with HIV in 2012. Mother-to-child HIV transmission (MTCT) accounts for more than 90% of pediatric AIDS cases. Despite the marked progress in coverage of prevention of mother to child HIV transmission (PMTCT) programs, high rate mother to child HIV transmission (MTCT) was documented among exposed infants. This raised questions about the effectiveness of PMTCT program and the need for more research on identifying predictors of MTCT. This study aimed to quantify MTCT rate and identify predictors among HIV-exposed infants at PMTCT clinic in Southwest Ethiopia.

Methods: A retrospective follow-up study was conducted at Jimma University Specialized Hospital (JUSH) PMTCT clinic from September 2011 to December 2013. Medical records of HIV-exposed infants and their HIV infected mothers were reviewed. Data were collected by a trained nurse working at the PMTCT clinic using a structured data extraction format. Data were then analysed by SPSS version 20. Univariate and multivariate logistic regression analyses were carried out to identify potential infant and maternal factors predicting mother to child HIV transmission.

Result: A total of 146 HIV exposed infants' and their mothers’ records were included in the final analysis. Majority, (83.6%), of HIV infected pregnant women were enrolled in ANC and 78.8% either were started on HAART or received a single dose of nevirapine (NVP) during labour. More than 80% of HIV-exposed infants received ARV prophylaxis (single dose of NVP plus AZT) for 7 days after birth. Out of 146 exposed-infants, 25 (17%, 95% CI: 11%-23.2%) were HIV positive. In the adjusted multivariate logistic regression analysis, mothers on late AIDS stage (stage 3 or 4) during child birth (OR=5.8; 95% CI: 1.6-16.5), absence of maternal PMTCT interventions (OR=4.9; 95% CI: 1.4-16.5), home delivery (OR=8.1; 95% CI: 2.1-31.9) and mixed infant feeding (OR=5.6; 95% CI: 1.4-41.2) were independently associated with mother to child HIV transmission among exposed infants.

Conclusion: We documented a high rate of mother to child HIV transmission among exposed infants on follow up at the PMTCT clinic in Southwest Ethiopia. All pregnant HIV positive mothers should be enrolled in PMTCT program at earlier stage and receive antiretroviral therapy. In addition, delivery at health center and exclusive
breast feeding should be encouraged so as to decrease mother to child HIV transmission.

No conflict of interest

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Modeling of HIV Transmission

The use of a mathematical model and risk ratio to estimate the impact of HIV/AIDS intervention programs on FSW and their communities: The Nigerian Experience

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Introduction: Having determined that Female Sex workers are one of the most important drivers of the HIV epidemic in Nigeria, a combination prevention program for Female Sex Workers (FSWs) was recently launched. As part of the evaluation of the impacts of these programs, a mathematical modelling Technical Working Group (MMTWG) was set up. The MMTWG developed a mathematical model to estimate the impact of the intervention programs on the rate of new infections among FSWs and their communities.

Objectives: The objective of the MMTWG is to develop a mathematical model to estimate how many indirect HIV infections will be inverted among FSWs, their clients and the general population, attributable to prevention programs targeting female sex works in Nigeria. The model was to also estimate the number of infections averted in all the intervention Local Government Areas ((LGAs), not only those in the Impact Evaluation (Control) areas. The mathematical model includes a risk ratio used to estimate the impact of the programme on new HIV infections among FSWs, number of new HIV infections in clients and members of the general population that were averted as a result of the effect of the intervention among the sex workers.

Methodology: A mathematical model (as shown in the appendix) was developed, using python programming language. Current values of the variables served as baseline inputs to the model. The variables include initial prevalence of HIV among FSW, their clients; proportion of sex acts that are protected; Initial population of the target group; duration of the intervention; number of sexual contacts per FSW and average number of sexual acts. A specific risk equation was developed for the FSW, incorporating the current values and projected values of the variable at the end of the program. Three Scenarios of the model was estimated over a period of five years. Putting all infected FSWs on treatment, irrespective of their CD4 or WHO staging and keeping other variables constant; Putting only eligible FSWs on treatment and increasing condom distribution; and universal access to treatment for all FSWs and their clients. An uncertainty analysis was also carried out as part of the model.

Results: It was observed that if the status quo (37% of eligible positive FSW on treatment) is maintained, the new infection rate will gradually increase to 3.6 in five years’ time. Putting 80% of eligible positive FSWs on treatment will avert 2789 new infections in the same duration and reduce the current rate of new infections to 0.7. A slight decrease of 0.3% would be experienced in the general female population. Putting all FSWs on treatment returns a 89.7% reduction on the number of new infections among clients of FSW.

Conclusion and Recommendations: The mathematical model reveals the efficiency of treatment in reducing the rate of new infections among FSWs, their clients and general female. The models reveals the importance of the investing in the FSW intervention programs now, rather in the future. The model outputs can be used to calculate the Quality Adjusted Life Years (QALY) to be gained during the intervention. A slight contribution of the total number of condom distributed to a reduction in new infection rate was also noticed. Further modelling scenarios are required to effectively infer on the efficiency of the intervention programs.

No conflict of interest

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Abstract: 35

Mother to Child Transmission

The mother-to-child transmission of HIV and Co-infection problem

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Introduction. The mother-to-child transmission of HIV in the absence of any interventions transmission rates range from 15-45%. This rate can be reduced to levels below 5% with effective interventions. Placenta plays an important role in the prevention of the mother-to-child transmission (MTCT) of HIV during pregnancy. The purpose of this study was to investigate the characteristics of the placetas and the expression of the CD14+ and CD68+ receptors in macrophages of the placenta of Russian HIV-infected women and to compare it with the expression of the immune receptors in placetas of women with co-infections and healthy women as controls.

Material & Methods. The study prospectively investigated postpartum placetas obtained from deliveries at two different (general and specializing in HIV-complicated deliveries women) maternity wards in St. Petersburg. The placetas were collected from three groups of patients: Group A – cases with children infected with HIV, Group B – cases with non-infected children born to HIV-infected mother and Group C – placetas from women without any infection. In morphological analysis routine staining (H&E) and microscope investigation were used. HIV-infection was confirmed immunohistochemically with use of ?24 antibodies. The DNA-viruses of family Herpesviridae was detected immunohistochemically with use of antibodies against HSV (I and II) and CMV. Receptors expression was studied immunohistochemically with use of monoclonal antibodies CD14 and CD68 and further morphometric analyses with the program Leica QWin Standard v2.8.

Results. The study collected 11 placetas in Group A, 11 placetas in Group B and Group C had 16 placetas. Placental infection was detected in 91% (n=10) of placetas Group A, 64% (n=7) of Group B. In Group A the majority of placental inflammation (73%; n=8) represented inflammatory changes, including 46% (n=5) combined bacterial and viral changes, and 27% (n=3) had isolated viral inflammatory changes – HIV and DNA-virus. In Group B the majority of placetas had HIV changes – 55% (n=6) and the smaller proportion – 18% (n=2) had combination of viral and bacterial infection associated changes. The presence of the bacterial and viral inflammatory changes was statistically associated with MTCT (p<0.05). The chronic insufficiency of placenta was detected in Group A in 46%, in Group B in 36%. Expression of CD14+ was the highest in Group A (14.14±1.11%), followed by Group B (10.04±1.37%), when compared with control Group C (3.21±0.43%, ?<0.05 for both comparisons). Similarly, the expression of CD68+ was the highest in Group A (13.07±0.83%), followed by Group B (7.21±0.89%) when compared to the control Group C (2.02±0.60%, ?<0.05 for both comparisons).

Conclusions: In our study there was a significant prevalence of bacterial and combined bacterial and viral inflammatory changes in the placetas of women with MTCT of HIV compared to the placetas of the women without MTCT. The presence of viral infections (HSV and CMV) and HIV was accompanied by the significant increase of CD14+ and CD68+ macrophages in the placenta of Russian women at time of delivery.

No conflict of interest
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Transmission of HIV Drug Resistance

Persistence of transmitted antiretroviral drug resistance mutations in the IAVI protocol C cohort

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Introduction: There is a paucity of data on viral diversity and evolution of transmitted antiretroviral drug resistant (TDR) HIV-1. The 29 individuals identified with TDR from the IAVI-Early HIV Infection Cohort (Protocol C) provide a unique opportunity to address this issue. This study characterized evolutionary mechanisms of antiretroviral drug resistant HIV-1 after transmission, and provided insights into persistence and/or rates of reversion in this cohort.

Methods: Viral RNA was extracted from longitudinal plasma samples (n=216) from 29 individuals with early HIV-1 infection from Kenya, Uganda, Rwanda, Zambia and South Africa with baseline TDR mutations (TDRMs identified by Sanger sequencing), RT-PCR amplified and sequenced on the Illumina Miseq. ARV drug resistance mutations on the CPR and Stanford HIV Drug Resistance Database were identified with the Exatype software (www.exatype.co.za; 1% cut-off).

Results: Data is currently available for 15 individuals. TDRMs identified by Sanger and MiSeq sequencing correlated, and additional minority variants were detected by MiSeq. TDRMs included K103N (n=7), M46L (n=1), I85V (n=1), Y188C (n=1), K103N and Y181C (n=1), K103E and E138A (n=1), A98G, E138Q, Y181C and M184V (n=1), K103N and E138A (n=1) and K103N, V108I and M184V (n=1). The TDRMs identified in 13 out of 15 individuals persisted in varying proportions for the follow up period (median:22.1 months, IQR:15.3-34.3). Sequenced virus from patient 10 showed reversion of K103E (64% to <1%) and E138A (75% to <1%) within three months, but G190A detected at baseline (24%) emerged as the predominant quasispecies by month 3 (99%), and persisted for the three year follow up. Virus from patient 20 showed persistence of K103N but reversion of V108I and M184V.

Conclusions: TDRMs appear to persist after transmission to a new host. Results highlight that understanding population dynamics of TDR HIV-1 in the absence of drug pressure is essential for clinical management, public health strategies and informing future vaccine design.

No conflict of interest

Abstract: 37

Virology of HIV Transmission

Diversity of HIV-1 proviral sequences during antiretroviral treatment from transmitted variants

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Background: In analyses of HIV-1 reservoirs, the relationship between transmitted HIV-1 and persistent proviruses has been understudied. Here we investigate 3 HIV-1 subtype C infections in Zambia-Emory HIV Research Project (ZEHRP) volunteers. These individuals were treated with antiretroviral drugs (ARVs) >2 years post-infection and achieved virologic suppression, with viral loads below 50 copies/mL.
Abstract

Materials & Methods: Near full-length HIV-1 genomes (NFLGs) from early infection (Fiebig stage III or earlier) were amplified from plasma and sequenced. NFLGs were also amplified and sequenced from white blood cell DNA during virologic suppression following 177-333 days of ARV treatment.

Results: In 2 individuals, a single variant was inferred as the transmitted/founder virus (TFV); in the third individual two variants were inferred as TFVs due to the presence of 2 phylogenetically distinct populations of approximately 96% sequence identity, and limited within-population diversity (<1%). Post-ARV proviral sequences showed an array of sequence diversity when compared to early infection sequences from the same individual. In the single-variant infections, post-ARV NFLGs showed 94-98% sequence identity to early infection sequences. In the case of multi-variant infection, proviral sequences formed a related cluster with >99% sequence identity, distinct from the early infection sequences but with greatest homology to just one of the two TFVs (97% vs. 95% sequence identity). Mutations observed in the proviral sequences include insertions and deletions up to 168 bp and APOBEC-mediated hypermutation.

Conclusions: Analysis of post-ARV proviruses from 3 HIV-1 infections indicates that multiple nucleotide polymorphisms are present that distinguish them from the TFV sequence. Ongoing investigations into the diversity of pre-ARV virus sequences and replication capacity will provide a clearer understanding of the relationship between transmitted HIV-1 and reservoir variants, and potential biases for archiving of virus in the reservoir.

Abstract: 38

Epidemiology of HIV Transmission

The geography of sex and HIV epidemics in sub-Saharan Africa: the case of Malawi

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Background: The majority of the HIV pandemic is located in sub-Saharan Africa where an estimated 25 million individuals are infected. In Malawi the prevalence of HIV amongst adults is ~11% (9% in men and 13% in women). The epidemic is predominantly driven by heterosexual transmission. Malawi has a population size of ~16 million. It is divided into three regions and 26 districts. There is considerable geographic variation in the epidemic (HIV prevalence ranges from <1% in the North to >20% in the South). We test the hypothesis that geographic trends in prevalence can be explained by geographic variations in community-level risk behavior.

Material & Methods: We use geo-referenced HIV testing and behavioral data from the 2010 Malawi Demographic and Health survey; a national representative survey based on a sample of 7,091 women and 6,497 men aged 15-49. We use geostatistical interpolation techniques to construct HIV prevalence maps separately for each gender. Similarly, we map the proportion of women and men in each community that engage in high-risk behavior. We define high-risk behavior as women with three or more lifetime sex partners and men with four or more lifetime sex partners. We calculate the degree of spatial association between areas of high-risk behavior and areas of high prevalence using local and global measures of spatial correlation, specifically we calculate the Moran’s index and plot cluster maps. We then conduct a regression at the district level, adjusting for spatial autocorrelation in the error, to quantify the extent to which community-level high-risk behavior explains local prevalence.

No conflict of interest
Results: Geographic variation in HIV prevalence in women varies from 1% to 29% (1% to 20% for men). Community-level high-risk behavior in women varies geographically from <1% to 40% (16% to 58% for men). Both HIV prevalence and community-level risk is higher in the South than in the North.

75% of the geographic variation in HIV prevalence in women is explained by variation in community-level risk behavior in women. Our regression predicts that if more than 18% of women in a community engage in high-risk behavior HIV prevalence in women will be above average.

Interestingly, geographic variation of HIV prevalence in men is better explained by variation in community-level risk behavior in women than by variation in community-level risk in men. 65% of the geographic variation in HIV prevalence in men is explained by community-level risk behavior in women. If more than 15% of women in a community engage in high-risk behavior HIV prevalence in men is predicted to be above average.

Conclusions: Geographic variation in community-level high-risk sexual behavior in women generates the large-scale spatial patterns in the HIV epidemic in Malawi, and can explain the North-South trend in increasing HIV prevalence. This has important implications for designing cost-effective prevention programs. There is a high degree of geographic variation in HIV epidemics in many other Sub-Saharan African countries. The reason for this has yet to be explained. Our study suggests a simple and plausible explanation.

No conflict of interest
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