9th International Workshop on HIV Transmission

Principles of Intervention

Abstracts
Oral presentations

Abstract: 1

Modeling Transmission and Interruption by PrEP

Expanding local HIV transmission networks highly contribute to spread of HIV in Utrecht, the Netherlands

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Background: Results of drug resistance testing for surveillance of transmitted drug resistance mutations (TDRM) and for clinical purposes in therapy-naive and therapy-experienced patients can provide valuable information to understand transmission dynamics of a local epidemic.

Methods: From 2004 until 2013, 709 adult newly diagnosed HIV-patients came into care at the University Medical Center Utrecht. Clinical and virological data was collected. *Pol* sequences of 663 (94%) therapy-naive patients were aligned with 212 *pol* sequences of therapy-experienced patients from the same center obtained in 2004-2013. A neighbor-joining phylogenetic tree was constructed (evolutionary model Tamura-Nei, 1000 replicates, MEGA6). Transmission clusters were identified using a threshold of bootstrap support of 95% and genetic distance <0.015. Subtyping was performed using COMET v0.5. TDRM was defined using the 2009 epidemiological list of the WHO.

Results: Of all HIV-patients entering care, the majority (84.9%) was male, of Dutch ancestry (73.9%) and the mean age at diagnosis was 39 years. The main route of transmission was MSM (65.6%), followed by heterosexual (HSX, 27.2%) and IV drug use (6.3%). Phylogenetic analysis showed that 354 therapy-naive patients (53.4%) were part of a transmission cluster. We identified 309 unique viral strains in the cohort, 67 small clusters (2-5 patients, n=290) and 19 large clusters (6-23 patients, n=193). 79% of the identified clusters (comprising 281 patients) consisted of only therapy-naive individuals. Based on available previous negative HIV test results of patients within the clusters, the mean duration of circulation of the viral strains from 18 large clusters was 48 months, with a range from 10 to 82 months. Most clusters (70/86) included patients who were infected with subtype B virus, the most prevalent subtype overall (70.1%). Phylogenetic analysis revealed one large cluster of 18 Dutch patients (11 MSM, 2 female HSX, 3 male HSX, 2 unknown) infected with subtype C virus.
Over 2004-2013, 11.9% of patients were infected with a virus harbouring TDRM (7.7% NRTI, 2.9% NNRTI, 3.5% PI). Phylogenetic analysis revealed three clusters with more than 6 patients infected with a virus with TRDM. Based on available previous negative HIV test results of patients within the clusters, the TDRM strains have been circulating for at least 3 years (T215S, 2009-2012), 4.5 years (M46L, 2005-2010) and 6 years (M41L, 2007-2013). Of patients infected with a virus with TDRM, 46.8% was part of clusters of only therapy-naive patients and 20.3% of clusters that also included therapy-experienced patients. Only 1 out of 3 strains with TDRM was a unique variant in our cohort. The three large TDRM clusters were accounting for 38% of all patients with TDRM.

Conclusion: Half of the newly diagnosed HIV patients in our clinical center were part of a transmission cluster, indicating local transmission highly contributes to the HIV epidemic in the area. Viral strains from large clusters were shown to be circulating up to nearly 7 years. Transmission of viruses harbouring drug resistance mutations is largely driven by transmission clusters that expand over time. These results suggest that active contact tracing may contribute to prevent new infections.

No conflict of interest

Abstract: 2

Modeling Transmission and Interruption by PrEP

Preclinical evaluation of TMC-278 LA, a long-acting formulation of rilpivirine, demonstrates significant protection from vaginal HIV infection

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Introduction: Vaginal HIV transmission accounts for the majority of new infections worldwide. Prevention efforts have demonstrated mixed success due to lack of adherence to drug regimens. New efforts to prevent HIV transmission have focused on long-acting (LA) antiretroviral drug formulations to circumvent this issue.

Methods: We first established critical pharmacokinetic parameters of intramuscular (IM) injection of TMC-278 LA in mice and demonstrated sustained drug release for 4 weeks. Humanized BLT mice were then vaginally challenged with HIV-1 transmitted/founder viruses (T/F) after IM administration of TMC-278 LA and the extent of protection from HIV acquisition was determined. In the 1st experiment, challenges with the T/F virus CH040 were performed 1 week after drug administration (600mg/kg). In a 2nd experiment, BLT mice were challenged 1 week after drug administration with 1 of 3 different viruses (CH040, RHPA, or JR-CSF). These mice were exposed to a second challenge 3 weeks after drug administration with a different T/F virus (THRO). Infection was determined using viral load assay and PCR analysis for vDNA in tissues. Identity of the infecting viruses was confirmed by DNA sequencing.

Results: In the first experiment, a single IM dose of TMC-278 LA (600mg/kg) one week before vaginal challenge provided significant protection from CH040 infection (6/6 mice protected) ($p=0.0047$). In contrast, 3/3 animals that received saline became infected. In the second experiment, 6/7 BLT mice that received saline before exposure became infected. Whereas 6/8 BLT mice that received TMC-278 LA before the first viral challenge were protected from infection ($p=0.026$). All mice exposed 3 weeks post-drug administration to a 2nd challenge with THRO became infected.

Conclusions: TMC-278 LA offers significant protection from vaginal HIV infection against T/F viruses. Although a wane in protection over time was observed. These results demonstrate the potential of long-acting antiretroviral formulations for HIV prevention.

No conflict of interest

Abstract: 3

Factors affecting the Bottleneck of Transmission

HSV-2 driven increase in a4ß7 correlates with increased susceptibility to shivsf162p3 infection ex vivo and in vivo

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Introduction: The availability of highly susceptible HIV target cells that can rapidly reach the mucosal lymphoid tissues may increase the chances of an otherwise rare transmission event to occur. $\alpha_4\beta_7^{high}$ $CD4^+$ T cells are particularly susceptible to HIV/SIV infection. They home to the gut and interact with HIV also through binding of $\alpha_4\beta_7$ to HIV-gp120. We hypothesized that HSV-2 modulates the expression of a_4b_7 and other homing receptors in the vaginal tissue and that this correlates with the increased risk of HIV acquisition in HSV-2 positive individuals.

Materials & Methods: To test this hypothesis we used an in vivo rhesus macaque (RM) model of HSV-2 vaginal infection (5 HSV-2 latently infected and 5 HSV-2 uninfected RMs) and we developed a new ex vivo model of macaque vaginal explants. We used 11-colors flow cytometry to determine the HSV-2 induced changes in the mucosa and a 29-Plex Luminex assay to identify soluble factors released by the HSV-2 infected tissues. We investigated which HSV-2 driven changes correlated with the HSV-2-driven increased susceptibility to $SHIV_{SF162P3}$ infection.

Results: In vivo we found that HSV-2 latently infected RMs were more susceptible to vaginal $SHIV_{SF162P3}$ infection and they had higher frequency of $\alpha_4\beta_7^{high}$ $CD4^+$ T cells in the vaginal tissue in absence of detectable HSV-2 replication. Similarly, ex vivo HSV-2 infection increased the susceptibility of the vaginal tissue to $SHIV_{SF162P3}$. HSV-2 infected tissues had higher frequencies of $\alpha_4\beta_7^{high}$ $CD4^+$ T cells and $\alpha_4\beta_7^{high}$ $CD80^+$ DCs. The increase directly correlated with HSV-2 replication. We found a higher amount of inflammatory cytokines in vaginal fluids of the HSV-2 latently infected animals similar to those found in the supernatants of the HSV-2 infected explants. Remarkably, the HSV-2-driven increase in the frequency of $\alpha_4\beta_7^{high}$ $CD4^+$ T cells directly correlated with SHIV replication in the HSV-2 infected explants.

Conclusions: Our results suggest that the HSV-2-driven increase in the availability of $CD4^+$ T cells and DCs that express high levels of $\alpha_4\beta_7$ is associated with the increase in susceptibility to SHIV due to HSV-2. This persists in absence of HSV-2 replication. Thus, a higher frequency of $\alpha_4\beta_7$ positive HIV target cells in the vaginal tissue may constitute a risk factor for HIV vaginal transmission.

No conflict of interest

Abstract: 4

Factors affecting the Bottleneck of Transmission

The sequence of the a4ß7-binding motif on gp120 of transmitted/founder viruses contributes to the dependence on the integrin for HIV infection

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Introduction: The integrin α4β7, which mediates the trafficking of T lymphocytes to the gut associated lymphoid tissue (GALT), a site of rapid HIV replication, has been described as an attachment factor for the V2 loop of the envelope protein gp120. We aimed to study the factors that influence dependence on α4β7 for replication of transmitted/founder viruses including cytokine levels in cervicovaginal lavage (CVL), STI infections and the sequence of the tripeptide α4β7-binding motif.

Materials & Methods: *All-trans* retinoic acid-activated CD4+ T cells were incubated with or without HP2/1 (anti-α4 antibody) or Act-1 (anti-α4β7 antibody) prior to adding virus. Infectious virus was prepared using envelope genes of the transmitted/founder (T/F) virus from 8 individuals in the CAPRISA Acute Infection cohort. Replication was monitored by p24 ELISA. Changes in viral sequence were generated by site-directed mutagenesis.

Results: T/F viruses with the highest dependence on α4β7 for replication had P/SDI/V motifs while those with lower dependence were LDI/L. Mutation of viruses with LDI/L motifs to P/SDI/V resulted in increased dependence on α4β7 for replication while the reverse mutation restricted the ability of the viruses to enter cells. T/F viruses from individuals diagnosed with bacterial vaginosis (BV) at the time of virus isolation had significantly higher dependence on the integrin for replication. Levels of IL-7, a cytokine that upregulates α4β7 expression, correlated with α4β7 dependence in the CVL shortly after transmission. Both BV status and high IL-7 levels in the CVL were associated with the P/SDI/V motifs in a larger cohort of 28 CAPRISA 002 participants.

Conclusion: P/SDI/V motifs are more common among South African HIV subtype C viruses accounting for 35% of variants. These data suggest that viruses with P/SDI/V motifs favour α4β7 reactivity at transmission influenced by the presence of BV and IL-7 cytokine levels. These findings may lead to vaccine and therapeutic opportunities in which α4β7 reactivity is exploited.

No conflict of interest

Abstract: 5

Biology and Immunity of Early Transmission

Transmission of pre-adapted viruses determines the rate of CD4 decline in seroconvertors from Zambia

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Introduction: HIV escapes adaptive cellular immunity by selecting mutations that are associated with the individual's HLA-I alleles. These mutations can be transmitted but the impact of this process on pathogenesis is poorly understood.

Materials & Methods: In 169 transmission pairs, we studied the transmission of HIV polymorphisms in Gag, Pol and Nef by Sanger sequencing of population amplicons in the donor (D) and the linked-recipient (LR) (≤3 months post-transmission). Polymorphisms statistically-linked to HLA alleles or located in well-defined CTL epitopes were quantified according to each LR's HLA alleles and associated with their set-point VL and CD4 counts.

Results: The majority of polymorphisms (83.6%) were transmitted from the D to the LR and a significant fraction (17.3%) was already adapted to the LR's HLA (11.6% escape and 6.2% epitope-located). A Spearman correlation analysis showed that transmission of Pol polymorphisms irrelevant to the LR's HLA was associated with a diminished set-point VL (p=0.003). This association was lost (p=0.4) when other variables known to determine set-point VL (gender-p=0.01; B*57-p=0.02; HLA-B sharing-p=0.006; replicative capacity (RC)-p=0.008) were included in a Generalized Linear Model. An in-depth analysis of survival curves (log-rank test) for different CD4 endpoints (200-350 cells/ul) showed that the proportion of transmitted HLA-linked polymorphisms relevant to the LR' HLA in Gag was consistently associated with a faster CD4 decline (p=0.0004). When other factors (gender, protective alleles, allele sharing, RC and set-point VL) were considered in a Cox Proportional Hazard Model, the proportion of transmitted HLA-linked polymorphisms in Gag remained the only variable significantly associated with CD4 decline (p=0.03).

Conclusions: Because most Gag, Pol and Nef polymorphisms are transmitted, newly infected individuals can receive a pre-adapted variant that leads to an accelerated disease progression (faster CD4 decline) without showing a significant effect on set-point VL.

No conflict of interest

Abstract: 6

Biology and Immunity of Early Transmission

No selection for Env with shorter variable loops in acute HIV-1 infection

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Introduction: Previous reports showed that HIV-1 viruses from early infection had shorter HIV-1 Env variable loops and could be more sensitive to neutralization. However, findings on HIV-1 subtype C and A were not confirmed with subtype B and there were uncertainties as to whether loop lengths evolved in the first weeks of infection. Here we characterized Env variable loops (V1-V5) in subjects newly infected (diagnosis at a median of 4 days after the last negative visit) with different HIV-1 subtypes.

Material & Methods: We sequenced 1,204 HIV-1 strains from 49 subjects enrolled in Kenya, Tanzania, Uganda and Thailand at a median of 4, 33 and 171 days after diagnosis. These sequences were compared to 624 independent sequences from chronic infection.

Results: Reflecting the distribution of subtypes in Thailand and East Africa, our cohort included individuals infected with CRF01_AE (n= 15), subtype A1 (n= 10), C (n= 4), and different A1/C/D recombinant strains (n= 17). V1 loops varied between 8 and 34 amino acid (AA) (IQR = 16-23), while V2 loops varied between 36 and 51 AA (IQR = 40-44). Variable loop lengths did not differ between HIV-1 subtypes ($p > 0.230$). Next, we compared loop lengths from our cohort to values from chronically infected subjects: for 280 sequences isolated past 2000, V1 loops varied between 5 and 42 AA (IQR = 18-24), and V2 loops between 36 and 74 AA (IQR = 40-45). There was no evidence that variable loops from acutely-infected individuals were shorter than those from chronically-infected individuals ($p > 0.188$). Finally, we found that Env variable loop lengths did not increase over the first six months of follow up in our cohort ($p > 0.352$).

Conclusion: Env sequences sampled in the first week of HIV-1 infection showed a wide range of variable loop lengths, making them undistinguishable from sequences from chronic infection. Our findings indicate that viruses with shorter Env variable loops are not selected for in the establishment of HIV-1 infection.

No conflict of interest

Abstract: 7

Biology and Immunity of Early Transmission

Increasing neutralization resistance over the course of the HIV-1 subtype C Southern African epidemic.

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Introduction: Understanding the neutralization properties of currently circulating viruses will aid in vaccine design. This study characterises the genotypic features and polyclonal neutralization susceptibilities of a large panel of functional transmitted / founder (TF) Clade C viruses from southern Africa collected over the previous ten years.

Materials & Methods: A total of 200 Clade C pseudoviruses were generated from samples collected over a 12 infection-year period (1998 to 2010) from five southern African countries, and tested against a panel of 30 serum from subtype C chronically infected South Africans. Phylogenetic- and hierarchical serum neutralisation-topology was compared by a permutation based approach and mantel test. Branch length from midpoint root was used as a measure of divergence and correlated with calendar year and serum susceptibility.

Results: The 200 clade C viruses phylogenetic tree had limited structure, and we found no evidence that the phylogenetic relatedness predicted neutralization sensitivity (permuation test, p=0.72; mantel test p>0.9). There was a negative correlation of neutralisation sensitivity with V1V2 hyper variable loop length (p<0.0001) and glycan density (p=0.0015); and a weak positive correlation with overall V1V2 net charge (p=0.0519). TF viruses contained significantly shorter V1V2 loop lengths (p=0.009) and less glycans (p=0.0099) compared to chronic viruses. We showed an increase in branch length over the course of the epidemic (p<0.00075) together with an accompanying decrease in neutralisation sensitivity (p=0.00047) as branch length increases.

Conclusions: Southern Africa clade C viruses shared neutralisation determinants suggesting that it will be possible to develop vaccines that provide regional coverage. Furthermore, TF viruses had distinguishing genotypic characteristics supporting previous findings that selection during heterosexual transmission takes place. Finally, we show that antigenic drift is detectable in the southern African Clade C epidemic suggesting that vaccines will need to be adapted over time to track viral divergence.

No conflict of interest

Abstract: 8

Sieving of Transmitted Viruses

HIV-1 of children with slow disease progression escapes autologous neutralization and triggers development of cross-neutralizing responses.

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Introduction: One-quarter of HIV-1 infected children has a disease progressing towards AIDS within the first year of age, whereas the majority of them progress slowly over several years. With the purpose to assess the role of the humoral immune response underlying different patterns of disease we studied the kinetics of antibody responses to HIV-1 and childhood vaccine antigens in slow and rapid progressors followed from birth to 5 years of age.

Material & Methods: Autologous and heterologous neutralizing capacity of plasma obtained during follow-up of 25 children was tested with PBMC- and/or TZMbl-assays, against up to 5 primary viruses for each child or 3 pseudotyped viruses (Tier 1 subtype B and Tier 2 subtype A), respectively. The seroreactivity to HIV-1 gp41, autologous gp120 V3-loop peptides, and tetanus and diphtheria toxoid was assessed by ELISA.

Results: Newborns displayed antibodies towards an immunodominant HIV-1 gp41 epitope, which were of maternal origin, but did not neutralize the transmitted virus. The child's neutralizing antibodies (Nabs) developed usually within 1 year of age to its own early virus concomitantly with autologous V3-loop directed antibodies in slow, but rarely in rapid progressors. Autologous Nabs persisted throughout disease progression and induced continuous emergence of escape variants. Heterologous Nabs developed within two years independently of disease progression, but their subsequent increase in potency and breadth was a preferential trait of slow progressors. Kinetics of antibody responses to the immunodominant gp41 antigens and childhood vaccine antigens was preserved independently of disease progression.

Conclusions: Persistent autologous Nabs triggering viral escape and increase in breadth and potency of heterologous Nabs are exclusive trait of slow progressors. Thus, immune-competence seems to impact the ability to develop potent Nabs, suggesting that early transmitted viruses of slow progressors represent an attractive target for vaccine design, which aims to induce cross-Nabs.

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No conflict of interest

Abstract: 9

Superinfection

CTL escape in variable Gag proteins associated with more rapid disease progression

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Introduction: The extent to which CTL escape mutations in acute/early subtype C infection influence long term disease outcome has not been well studied. We investigated the effect of CTL escape in Gag during the first year of infection on disease progression over five years.

Materials & Methods: Viruses from 78 HIV-infected study participants from the CAPRISA 002 cohort were sequenced in the Gag region at enrolment (earliest available sample) and 12 months post-infection. Evidence of CTL escape was identified using a list of HLA-associated polymorphisms generated from a large subtype C chronic dataset. CTL escape was defined as a mutation occurring between the enrolment and 12 months sequences at HLA-associated sites with respect to the participants' HLA genotype in the following manner; 1) towards an HLA adapted amino acid residue, and 2) away from a non-adapted amino acid residue.

Results: All subjects were infected with subtype C viruses. The median (IQR) time post-infection for the enrolment samples was 41 (28-55) days. We observed escape mutations in 48 (62%) of the study participants. When stratified according to Gag proteins, escape was observed in 33 (42%) participants in p17, 22 (28%) in p24 and 14 (18%) in p7p6. There were associations between potential and observed HLA-associated mutations in the more variable Gag proteins [p17 (Spearman R=0.2; p=0.06) and p7p6 (Spearman R=0.2; p=0.07)] and not in the conserved Gag protein [p24 (Spearman R=0.09; p=0.4). Furthermore, individuals whose virus escaped in variable proteins (p17 and p7p6) progressed more rapidly to CD4+ decline to 350 cells/ul over 5 years, compared to those whose viruses developed p24 escape mutations [the order of progression; no escape > p24 escape > p7p6 escape > p17 escape (p=0.06; Kruskal-Wallis test]. Individuals showing escape in p24 tended to have higher CD4+ counts at 12 months post-infection (p=0.09; Mann Whitney test).

Conclusions: These results suggest that escape in Gag is associated with increased disease progression. However, escape in the more variable p17 and p7p6 is associated with more rapid CD4+ decline compared to escape in the more conserved p24 region. Constraints in the p24 region may be limiting escape in acute/early infection. This underscores the importance of HLA-driven immune selection in shaping HIV evolution over the disease course and further supports targeting of p24 in CTL-based vaccine designs.

No conflict of interest

Abstract: 10

Superinfection

The effect of HIV-1 superinfection on the humoral immune response

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Background: A better understanding of how neutralizing antibody responses develop during natural infection and the factors that augment them could be instrumental in the design of improved immunogens and immunization protocols. HIV superinfection (infection by a second HIV strain following seroconversion to an initial HIV infection) provides a unique opportunity to evaluate whether sequential infection and antigenic diversity can enhance the breadth and potency of elicited anti-HIV antibody responses.

Methods: Neutralization breadth in three HIV-1 superinfected participants was compared to that of 17 singly-infected participants using a panel of 44 heterologous viruses. Autologous plasma neutralizing titers and specificity were also assessed longitudinally in three superinfected and three co-infected (infected with two strains, both prior to seroconversion) participants. Neutralizing responses to both primary and superinfecting viruses were assessed longitudinally, and mapped.

Results: HIV superinfection alone was not sufficient to broaden neutralizing antibody responses. However two of the three superinfected participants developed extremely high neutralizing titers against the superinfecting virus, with ID_{50} values exceeding 1:20,000 and 1:40,000 respectively. None of three co-infected participants generated similarly elevated titers suggesting that sequential infection was a driving factor. As titers to the primary variants were not concomitantly boosted the mechanism was likely distinct from the anamnestic response. This was supported by epitope mapping experiments, which indicated that the targets of the neutralizing antibody responses to the superinfecting viruses were not conserved in the primary viruses. Neutralizing titers to the primary infecting viruses fell as titers to the superinfecting viruses rose suggesting that there may be competition between responses to related but distinct Envelopes. In support of this, one co-infected participant (CAP267) preferentially neutralized one of two infecting variants, with weak or no titers to the second variant over time.

Conclusion: Taken together, these data indicate that while exposure to multiple Envelopes may promote potent neutralizing antibody responses, it may not broaden the coverage of these responses. Rather, the neutralizing antibody response to one Envelope may occur at the expense of responses to the other. This has significant implications for the use of polyvalent immunogens.

No conflict of interest

Abstract: 11

Abstract driven Presentations

Antibody inhibition of HIV-1 transmission from antigen-presenting cells to CD4 T lymphocytes involves immune cell activation

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Background: The mucosal tissues contain various HIV target cells including antigen-presenting cells (APCs) such as Langerhans cells (LCs), interstitial dendritic cells (iDCs) or plasmacytoid (pDCs) in addition to CD4 T lymphocytes. These APCs play a major role in HIV-1 dissemination. Broadly neutralizing antibodies (bNAbs) need to impair HIV-1 cell-to-cell transmission to efficiently protect from HIV-1 transmission at the mucosal site. The aim of this study is to decipher the mechanisms by which Abs protect from HIV-1 transfer.

Methods: We used a physiologically relevant model of primary APCs, infected with R5 HIV-1 isolates or transmitted/founder virus HIV-1_{Bx11}, cocultivated with autologous CD4 T cells in the presence or absence of bNAbs. At 48 and 72h post-infection, the percentages of infected cells, the expression of intracellular SAMHD1 and $CD83^+$/$CD86^+$ maturation markers were determined by flow cytometry. IFN-α production was measured in the culture supernatant. Statistical analysis was performed using the Two-tailed Paired t test, and the groups were compared by one-way ANOVA (Kruskal-Wallis test) with $P < 0.05$ is considered significant.

Results: We found that APCs efficiently transferred HIV-1 to adjacent CD4 T cells. Interestingly, coculture with CD4 T cells downregulated SAMHD1 expression in DCs (e.g. for pDCs: p=0.0463), enhanced HIV-1 replication (p<0.0001), induced DC maturation (CD83 on pDCs: p=0.0005; CD86 on pDCs: p=0.0004) and increased IFN-α secretion (p=0.0326). bNAbs efficiently prevented HIV-1 transfer to CD4 T cells with a similar efficiency as cell-free infection. Moreover, DC maturation and IFN-α production were modulated by Abs. For example, bNAb VRC01 did not impair DC maturation and IFN-α secretion, whereas 4E10 increased immune cell activation. This Ab-associated modulation of APC activation participates to the overall Ab inhibition of HIV-1 transmission.

Conclusions: During HIV cell-to-cell transmission, crosstalk between APCs and autologous CD4 T lymphocytes occurs leading to increased HIV replication, immune activation and immune sensing. HIV-1-specific Abs modulate these immune functions, therefore interfering with HIV-1 transmission. Consequently, this additional Ab function should be taken into consideration for the design of new vaccine strategies.

No conflict of interest

Abstract: 12

Abstract driven Presentations

HIV-susceptible target cells in foreskins from medical male circumcision in South Africa: Markers of HIV risk?

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Introduction: Medical Male Circumcision (MMC) reduces the risk of HIV acquisition by up to 60%, confirmed in a number of large clinical trials throughout Africa. MMC has also been shown to reduce the prevalence of other sexually transmitted infections (STIs), which in turn may impact HIV acquisition.
We hypothesized that the underlying mechanisms for this protection may be removal of potential target cells for HIV infection and altered levels of keratinisation in men after MMC.

Materials & Methods: In a longitudinal study involving 2 clinical sites and 150 participants within South Africa, we investigated CD4+ T cell frequencies by flow cytometry and immunofluorescent imaging in a subset of 10 HIV negative individuals (14 – 24 years) undergoing elective MMC at Edendale Hospital in Kwa-Zulu Natal and at the Perinatal HIV Research Unit in Soweto, Johannesburg. We compared the levels of keratinisation between the inner and outer foreskin and assessed the impact of STIs (*C. trachomatis*, *N. gonorrhoea, M. genitalium*, *T. vaginalis, HSV-1 & 2*) on HIV target cell density in foreskin tissues. Tanner staging and testosterone levels were measured in all men included in the study.

Results: Flow cytometry showed that the inner foreskin on these young HIV negative men had higher frequencies of CD4+ T cells compared to outer foreskins. Preliminary immunofluorescent staining for CD4, Ki67 and CD207 to identify proliferating immune cells and filaggrin for keratin layers showed elevated numbers of both CD4+ T and CD207+ Langerhans cells in the foreskin of men with STIs compared to those without an STI.

Conclusions: MMC may reduce the risk of HIV infection in this highly susceptible age group of men by removing the potential CD4+ HIV target cells present in foreskins of young uncircumcised men in South Africa. STI-induced inflammation and recruitment of immune cells to the foreskin, may be elevating the risk of HIV acquisition in uncircumcised men.

This study was supported by a Strategic Primer Grant from the EDCTP and additional funding from the CAPTN and SA MRC.

No conflict of interest

Abstract: 13

Abstract driven Presentations

Transmitted HLA escape mutations lead to accelerated HIV-1 disease progression and largely define the relative contribution of HLA alleles to control

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Background: The extent of intra- and inter-host adaptation of HIV to the HLA-mediated immune responses remains a central challenge for vaccine design, as the presence of escape mutations in circulating HIV sequences may compromise vaccine-induced immunity and reduce the protective effects of certain HLA alleles. One strategy is to vaccinate against escaped epitopes, though it is unclear whether such epitopes can elicit effective immune responses.

Material & Methods: We developed a probabilistic model of HIV sequence evolution, trained on >4,000 clade B and C sequences with matched HLA types, that yields a natural metric of the extent of HLA-specific adaptation of each sequence. Intra-host HIV adaptation to HLA was strongly associated with VL and CD4 counts in cross-sectional and longitudinal early infection cohorts, validating our models and confirming the role autologous adaptation plays in disease progression.

Results: Within transmission pairs, the extent to which the donors' Gag, Pol and Nef sequences were 'pre-adapted' to the linked recipients' HLA alleles predicted recipient VL 24 mo post infection (Spearman ρ=0.39, p=0.0005, N=81) and time to CD4<250 (HR = 5.97, p = 0.03, N=48). In cross-sectional chronic cohorts, individuals for whom the regional circulating viral sequences were well adapted ('inter-host adaptation') had higher viral loads. Inter- and intra-host adaptation independently contributed to VL prediction and together explained twice as much variance in outcomes as all HLA alleles combined (p<1E-10, linear mixed model). Consistent with this observation, the extent to which circulating HIV strains were adapted to individual HLA alleles predicted the mean VL associated with expression of those alleles (Spearman ρ=0.77, p=0.009, among the 10 alleles significantly associated with VL) in the clade B chronic infection cohort. Among five chronic infection clade C cohorts from three southern African countries, inter-host adaptation to specific alleles consistently predicted how protective the alleles were, both among HLA alleles within a cohort and among cohorts for the same HLA allele, explaining 22% of the overall variance among significantly protective or hazardous HLA alleles (p=0.001, linear mixed model).

Conclusions: Transmission of HIV pre-adapted to host HLA leads to accelerated disease progression and largely explains the extent to which an HLA is relatively protective or hazardous. That this effect remains an independent predictor of VL well into chronic infection suggests transmission of escaped epitopes results in a permanently impaired immune response. This observation argues that the immune system is unable to mount effective responses against these adapted epitopes, even when they represent the initial challenge variant, and suggests that vaccination strategies that target such adapted epitopes must achieve a level of response that is not observed in natural infection.

No conflict of interest

Abstract: 14

Abstract driven Presentations

Semen-mediated enhancement of HIV infection markedly impairs the antiviral efficacy of microbicides

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Background: Topically applied microbicides potently inhibit HIV in vitro but largely failed to exert protective effects in clinical trials. Here, we explored whether the ability of semen to enhance HIV infection affects the antiviral efficacy of various classes of microbicides and antiretrovirals (ARVs).

Methods: HIV infection assays were performed in the presence or absence of semen (or synthetic amyloid fibrils) in cell lines and primary CD4 cells; IC50 values of ARVs that target various steps of the viral life cycle were determined and evaluated.

Results: We demonstrate that the ability of semen to enhance HIV infection in vitro markedly impairs the antiviral efficacy of ARVs that target virion components, by 10 to 20-fold. These ARVs include polyanions, neutralizing antibodies, NRTI and NNRTI's, and inhibitors against HIV-1 Integrase and Protease. Similar results were obtained using synthetic SEVI amyloid fibrils. In contrast, semen deficient of amyloids and lacking the ability to enhance HIV infection did not impair the antiviral activity of ARVs. In direct contrast, the CCR5 antagonist Maraviroc (MVC) blocked untreated and semen-exposed virus with similar efficacy. Notably, the concentrations of MVC required to block semen-exposed virus are lower than those that can be achieved in the genital tract after oral administration of the drug.

Conclusions: Our data show that the HIV enhancing activity of amyloids in semen undermines the antiviral efficacy of ARVs that target viral components, which might explain why such microbicides largely failed in clinical trials. In contrast, MVC, which targets a host protein, retained activity in the presence of semen, suggesting that compounds targeting cellular components may be advantageous for microbicide development. Since semen is the main vector for HIV transmission, we recommend testing candidate microbicides against semen-exposed virus to identify agents that retain potent activity during sexual virus transmission.

No conflict of interest

9th International Workshop on HIV Transmission

Principles of Intervention

Abstracts
Poster presentations

Abstract: 15

Behavioral risk factors affecting HIV Transmission

Contextual gender based behavioural risk factors of HIV transmission in Nigeria

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Background: Gender inequality has been identified as a key driver influencing the vulnerability of women and girls to HIV infection. This is evident in the current HIV prevalence among the general population in Nigeria (3.4%) of which women constitute 59%. Consequently the National Agency for the Control of AIDS (NACA), Nigeria carried out a gender assessment of the National HIV and AIDS response with the aim of facilitating learning about the extent to which the national response recognizes and acts on gender inequality as a critical enabler of the HIV and AIDS epidemic. The assessment equally identified strategic investment options that would enable gender mainstreaming in the national HIV response.

Methods: NACA constituted a Gender Assessment Team (GAT) to lead the process. The team included relevant development and implementing partners; community-based organizations (CBOs); the public and private sectors. Joint United Nations Programme on HIV/AIDS (UNAIDS), Nigeria office provided technical and financial support. The UNAIDS gender assessment tool was the framework for the assessment. A review of over 100 national HIV documents and websites was conducted. A data collection workshop was also conducted for national stakeholders selected from the six geopolitical zones of the country to collect information about socio-cultural gender inequality issues that act as critical enabler for HIV and AIDS. The participants at the workshop also identified challenges and opportunities for gender mainstreaming at the community level in HIV/AIDS response. Data analysis was carried out using quantitative and qualitative methods to identify socio-culturally predisposing risky behaviours for males and females. The analysis equally identified gender gaps and human rights issues in laws and regulations related to HIV policies, strategies, guidelines and services in the country.

Results: Contextual factors contributing to risky behaviours that predispose women to the epidemic comprised of poverty, child marriage, gender-based violence, masculinity and femininity norms, disabilities, harmful traditional rites as well as human rights, legal and political factors. The Assessment also revealed that gender inequalities and low socio economic status of women in Nigeria continues to fuel their susceptibility to HIV infection as well as the increased burden of AIDS. Huge gaps exist in the understanding of the gender dynamics of the HIV and AIDS epidemics and its interplay with human rights violations across board. Most HIV/AIDS interventions do not have specific budget to address gender gaps.

Conclusion: The assessment was wide-ranging and provides a suitable evidence informed baseline for improving the strategies to address the HIV epidermic in Nigeria. Strengthening systemic, legal and social transformative interventions regarding gender inequalities as it relates to the national HIV and AIDS response are recommended at all levels. Resource allocation and budgetary provision to specific gender responsive interventions are of paramount importance for gender mainstreaming in the national HIV response.

No conflict of interest

Abstract: 16

Behavioral risk factors affecting HIV Transmission

Reducing HIV behavioral risks for out-of-school, 15-24 year old girls in Mukuru Slums, Nairobi through the Bold Idea for Girls (BIG) project.

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Introduction: More than 60% of new HIV infections in Kenya occur among young people aged between 15-34 years (*Kenya National AIDS Strategic Plan 2009/10-2012/13, 2009*). In Kenya, young women aged 20-24 years are over three times more likely to be infected than young men of the same age group—the prevalence being 4.6% and 1.3% respectfully (*Kenya AIDS Indicator Survey, 2012*). This is compounded by the observations that girls are less likely to access services offered by health programs (*Weiss et al, 2000*).Studies have shown association between reduction of HIV incidences with reduction of the number of sexual partners and increased condom use among the youth (*Asiimwe et.all, 1997*). A study with 15-24 year old youths in South Africa recommended promotion of partner reduction, consistent condom use and prompt treatment for sexually transmitted infections while addressing structural factors that make it difficult for the youth to implement behavior change (*Pettifor et al, 2005*). Provision of economic empowerment interventions have been found to reduce sexual risks of urban slum girls (*Odek, W et all, 2009).*
*H*OPE worldwide Kenya is collaborating with the University of Nairobi Center for HIV Prevention and Research to implement a one year pilot project dubbed Bold Idea for Girls (BIG). The Grand Challenges Canada –funded project targets out-of-school girls aged 15-24 years old in Mukuru Slums in Nairobi and integrates HIV prevention, gender and economic empowerment aspects. The project aims to increase adoption of safer behaviours by increasing access to and uptake of HIV prevention interventions. This paper looks at the self-reported changes in behaviour by the girls participating in the project. The findings will inform approach by programs offering sexual and reproductive health and rights (SRHR) interventions for girls in resource-poor settings.

Methods: In November 2013, 523 15-24 year old girls were enrolled into the BIG project. Behavioural data was collected and reported as proportions at baseline and midterm levels. A regression model was used to determine any differences in self-reported behaviour (health/health information-seeking, reduction in number of sexual partners; and correct and consistent condom use) between the two levels.

Results: The girls who had tested for HIV in the last three months increased from 1% at baseline to 53% at midterm (OR 75.83; 95% C.I 26.22-219.31; p<0.0001), and those who sought information from HIV programs increased from 41% to 89% (OR 11.68; 95% C.I 6.10-22.38; P<0.0001). Among the sexually active girls, self-reported correct and consistent condom use during sex increased significantly from 13% to 68% (OR 14.22; 95% C.I 8.70-23.24; p<0.0001). There was also a significant reduction of the proportion of girls who had more than one sexual partner from 16% to 2%.

Conclusion: The integrated BIG project seem to be helping to improve health/health information-seeking behavior; reduce the number of sexual partners and increase correct and consistent use of condoms among the 15-24 year old girls in Mukuru Slums. Programs offering SRHR interventions for girls in resource-poor settings are encouraged to consider integrating HIV prevention, gender and economic empowerment aspects.

No conflict of interest

Abstract: 17

Behavioral risk factors affecting HIV Transmission

Venue preferences and the association with HIV prevalence and testing uptake among male sex workers in Shenzhen, China

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Introduction: Chinese male sex workers, also called money boys (MBs), are a subgroup of men who have sex with men (MSM). They are at high risk of acquiring and transmitting HIV.

We aim to determine whether MBs preferring certain venues for seeking sex partners differ in socio-demographic characteristics and sexual behaviors, and whether venue preference is a significant determinant for HIV prevalence and testing uptake.

Methods: We conducted a cross-sectional survey in Shenzhen city, South China, using time-location sampling. We performed chi-square analysis to compare characteristics of MBs preferring certain venues, and we used logistic regression to identify determinants of HIV prevalence and testing uptake.

Results: Characteristics of demographics and sexual behaviors of MBs clearly depend on self-reported venue preferences. MBs preferring saunas were more likely to self-identify as bisexuals, have sex with both sexes, and use condoms inconsistently. Venue preference, however, is not associated with HIV prevalence and testing uptake. Being married and self-identifying as homosexuals were associated with a higher HIV prevalence; having 1 to 10 anal partners and no access to HIV services were associated with a lower uptake of HIV testing.

Conclusions: MBs preferring different venues have no difference in HIV prevalence and testing uptake, yet the riskiest seem to be those preferring saunas. We recommend public health officials to target saunas to reduce HIV risk behaviors of MBs and promote HIV-related services.

No conflict of interest

Abstract: 18

Behavioral risk factors affecting HIV Transmission

Impact of persistent Human Papillomavirus (HPV) infections on inflammatory cytokine levels in the female genital tract: implications for HIV risk

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Background: Women with persistent HPV-infections are at increased risk for developing cervical cancer. Clearance of HPV-infections has been associated with genital inflammation. HPV infection has been shown as a risk factor for HIV acquisition along with genital inflammation. The aim of this study was to evaluate the impact of genital tract inflammation and HPV persistence or clearance in HIV negative women.

Methods: Cervical samples were collected from 38 HIV-negative women at twice, six months apart. IL-8, IL-6, IL-10, IL15, IL-12p40, IP-10, MCP-1, MIP-1a, MIP-1b, IL-1a, IL-1b, eotaxin, fractalkine, and G-CSF concentrations were measured by Luminex at enrollment. HPV types were assessed at both time points using the Roche Linear Array HPV Genotyping assay.

Results: There were 20/38 infected women at enrollment [9 of whom had high-risk (HR) and 11 low-risk (LR) types]. An additional 7 acquired an HPV infection over the 6 months of follow-up. Of the 20 initial HPV infections only 2 cleared their infections while18 infections persisted for 6 months. Women with HR HPV at enrollment generally had higher cytokine concentrations in their genital tracts than women with LR types, although none of the cytokine evaluated were significantly different between groups. Women acquiring an HPV infection over 6 months had lower overall genital inflammation compared to women who remained HPV-negative (p=0.005). In contrast, women with persistent HPV infections generally had increased inflammation at enrolment compared to women who remained negative (p=0.049).

Conclusion: Although HPV infection has been associated with increased risk for HIV infection, we found
that HPV infections generally did not cause an inflammatory response in the female genital tract.

No conflict of interest

Abstract: 19

Biology of HIV Transmission

HIV-enhancing amyloids are prevalent in fresh semen and are a determinant for semen's ability to enhance HIV infection: relevance for HIV transmission

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Introduction: Semen, the most common vehicle for HIV transmission, enhances HIV infection *in vitro*. Previously, naturally-occurring peptides derived from the semen proteins prostatic acid phosphatase (PAP) and semenogelin (SEM) were shown to polymerize into amyloid fibrils that markedly enhance HIV infection. Here, we investigated whether endogenous amyloid fibrils can be detected in fresh semen, and if so the extent to which they contribute towards the ability of semen to enhance HIV infection.

Materials & Methods: Confocal microscopy, electron microscopy, atomic force microscopy, quantitative mass spectrometry, ELISAs, and viral infection assays were used to detect, quantitate, and characterize endogenous HIV-enhancing amyloids in semen.

Results: Endogenous PAP and SEM amyloids were directly visualized in unmanipulated semen by immunogold electron microscopy and confocal microscopy. Amyloid structures were further characterized by atomic force microscopy. We additionally demonstrated that endogenous amyloids are present in semen from men acutely infected with HIV, and that these fibrils directly bind HIV virions. We then examined whether the extent to which semen enhances HIV infection correlates with the levels of endogenous amyloids. We found that the magnitude of HIV-enhancing activity of semen is dependent on the semen donor and the degree of liquefaction, and that the levels of the HIV-enhancing PAP and SEM amyloidogenic fragments significantly correlate with the variability in enhancing activity observed between samples. Accordingly, semen completely deficient in amyloids, due to a condition termed ejaculatory duct obstruction (EDO), lack the ability to enhance HIV infection.

Conclusions: Our results demonstrate that endogenous semen amyloids are a crucial determinant for semen-mediated enhancement of HIV infection, and emphasize the need to consider the effects of semen in approaches to minimize the spread of HIV.

No conflict of interest

Abstract: 20

Biology of HIV Transmission

Vaginal concentrations of lactic acid potently inactivate HIV-1 compared to short chain fatty acids present during bacterial vaginosis

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Introduction: Bacterial vaginosis (BV) is caused by an imbalance in vaginal microflora and is a major risk factor for sexually transmitted infections, including HIV in women. Microflora composition is likely influenced by low vaginal pH (~3.8), maintained by racemic

DL-lactic acid (LA) (~110mM). BV alters the pH (>4.5) and the short chain fatty acid (SCFA) profile to predominantly acetic acid (BV) vs LA (non-BV). Our previous studies highlight the potent HIV virucidal activity of LA; however, the virucidal activity of BV-associated SCFAs is unknown.

Materials & Methods: Virucidal activity of physiologically relevant non-BV associated SCFAs at pH 3.8 versus BV-associated SCFAs at pH 5 were compared against subtype B transmitted/founder (T/F) strains, RHPA and CH058, subtype C 92BR025 and subtype EA CMU02. Anti-HIV activity of 100mM of DL-LA (pH3.8) and 100mM of acetic acid (pH 5) was determined over time. The structure activity relationship (SAR) of SCFAs and HIV-1 virucidal activity was assessed at the same pH and at equal concentrations of the active protonated forms.

Results: Non-BV associated SCFAs (pH3.8) rapidly inactivated T/F strains causing a 1000-fold drop in HIV-1 infectivity while BV associated SCFAs (pH5) caused little inactivation. This potent virucidal activity could be attributed to DL-LA (a non-BV SCFA), and not low pH. DL-LA had the greatest virucidal activity against subtypes B, C and EA over related BV-associated SCFAs at the same pH and concentration of the active form. SCFA SAR analysis revealed potent virucidal activity is associated with the presence of hydroxyl groups, especially on the α-carbon; which is attenuated by the presence of a CH_3 group on the carboxylic acid.

Conclusions: We show that LA, a non-BV SCFA, is a more potent HIV virucide than SCFAs produced during BV, suggesting that BV-associated SCFAs are not as protective for the female reproductive tract. SAR analysis reveals chemical elements required for HIV-1 activity that could inform the design of SCFA analogues.

No conflict of interest

Abstract: 21

Biology of HIV Transmission

Lactic acid, a vaginal microbiota metabolite, elicits an anti-inflammatory response from vaginal and cervical epithelial cells

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Introduction: *Lactobacilli sp.* dominate the vaginal microbiota in about 1/3 of reproductive age women and HIV susceptibility increases with a shift from lactobacilli to bacterial vaginosis (BV) associated bacteria. Lactobacilli acidify the vagina to pH<4.0 by producing ~1% lactic acid (LA) in a nearly racemic mixture of D and L isomers. Epithelial cells that line the vagina and cervix have barrier and immune functions in the lower female reproductive tract (FRT). Here we investigate the immune modulatory effects of LA on epithelial cells from the lower FRT that might play a role in decreasing HIV susceptibility.

Materials & Methods: The effect of LA in the apical medium was assessed on vaginal (VK2), endocervical (End), ectocervical (Ect) epithelial cells and primary ectocervical cells grown in transwells. Toxicity effects were determined by viability staining and diffusion of fluorescently labelled dextrans through the cell layer. Cytokine profile from epithelial cells was determined following stimulation with toll-like receptor (TLR) agonists ± LA.

Results: L-LA (0.3%; pH 3.9) had little impact on VK2, End and Ect monolayer toxicity. Stimulation of all epithelial cell lines with poly(I:C)(TLR3) induced high-levels of pro-inflammatory cytokines IL-6 and IL-8, and their variable induction with TLR agonists Pam(3)CSK(4)(TLR1/2) and lipopolysaccharide (TLR4). In contrast, the presence of 0.3% L-LA or D-LA either significantly abrogated or reduced TLR-induced IL-6 and IL-8 secretion by epithelial

cell lines. Irrespective of the TLR agonists, L-LA and D-LA elicited high-levels of the anti-inflammatory cytokine IL-1RA (~30,000 pg/ml) from all cell lines. Neither 0.3% L-LA at neutral pH nor acidity alone (HCl) increased IL-1RA or decreased TLR induced IL-6 and IL-8 production indicating that the immune modulatory effect of LA is mediated by the protonated form of LA and that the effect is not simply due to acidity. L-LA (0.3%; pH 3.9) also dramatically reduced poly (I:C) induced expression of IL-6, IL-8, TNFa, RANTES and MIP3a in primary ectocervical epithelial cells.

Conclusions: LA at pH 3.9 found in lactobacillus-dominated vaginal microbiota elicits an anti-inflammatory effect on lower FRT epithelial cells and inhibits inflammation induced by bacterial and viral TLR agonists suggesting a role in mitigating inflammation-induced HIV susceptibility at the genital mucosa.

No conflict of interest

Abstract: 22

Biology of HIV Transmission

Immune activation and HIV target cells in the adolescent female genital tract

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Introduction: The biological mechanisms underlying HIV risk in younger women is unclear. As HIV is primarily transmitted across the genital mucosa and preferentially infects activated $CD4^+$ cells, we investigated the influence of age and sexually transmitted infections (STIs) on $CD4^+$ target cell immune activation from the genital tract of adolescent females from South Africa.

Methods: As part of a longitudinal cohort study aiming to enrol 150 adolescent women between the ages of 16-22 years at the Desmond Tutu Youth Centre, Masiphumele, Cape Town [part of the EDCTP funded Women's Initiative in Sexual Health (WISH)], cervical mononuclear cells were obtained from 35 adolescents and the T-cell expression of activation and proliferation markers (CD38, HLA-DR, Ki67) was measured by FACs. Women were screened for bacterial vaginosis (BV) and STIs (*C. trachomatis*, *N. gonnorhoea*, *T. vaginalis*, *M. genitalium*, HSV-1 & 2 and HPV). For comparison, 11 HIV-negative adult women were also included.

Results: Adolescents (median 18 years; IQR 18-19) had significantly higher frequencies of activated $CD4^+$ T-cells ($CD38^+$, $HLADR^+$, $CD38^+HLADR^+$: each $p<0.0001$) than adult women. In contrast, adolescents had significantly lower frequencies of $CD4^+$ T-cells expressing CCR5 ($p=0.02$) than adult women. When adolescents were stratified according to age (16-17, 18-19 and 20-22 year old), the 16-17 year old females generally had higher levels of activated and proliferating T-cells compared to the other age groups, significantly so for the proliferating $CD4^+$ T-cells (Ki67+; ANOVA: $p=0.048$). The prevalence of STIs and BV were high in adolescents, with 40% testing positive for *C. trachomatis*. Adolescents infected with *C. trachomatis* tended to have higher levels of T-cell activation compared to those without an STI, significantly so for $CD38^+HLADR^+$ T-cells ($p=0.01$).

Conclusion: Heightened levels of genital immune activation found in South African adolescent females, partly due to the presence of STIs, could put them at higher risk of HIV infection.

No conflict of interest

Abstract: 23

Biology of HIV Transmission

Impact of systemic immune activation and inflammation on the HIV susceptibility of HIV- individuals with HIV concordant or discordant partners

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Introduction: Studies of individuals who appear to resist HIV infection, such as HIV- partners in HIV discordant relationships, are important for identifying host responses or characteristics associated with protection against HIV infection. Previously, immune quiescence has been associated with HIV resistance. The aim of this study was to compare the level of IA and systemic inflammation in HIV- individuals from South Africa (SA) who were either in relationships with HIV-infected or uninfected stable partners, to evaluate markers of HIV exposure or resistance.

Materials & Methods: A heterosexual couples cohort of 103 HIV- individuals with long-term stable HIV- concordant partners (HIV- unexposed) and 113 HIV- individuals with HIV+ discordant partners (HIV- exposed) were included in this study. T cell activation and proliferation (CD38, HLA-DR, CCR5, Ki67) in blood was assessed by flow cytometry. Cytokines in plasma were evaluated by Luminex.

Results: HIV- exposed individuals had lower frequencies of CD4+ T-cells in blood expressing the CCR5 [alone (p=0.05) or in combination with Ki67 (p=0.05) or CD38 (p=0.05)] than HIV-unexposed individuals. Similarly, HIV- exposed individuals had significantly lower frequencies of CD8+ T-cells in blood expressing CCR5 [alone (p=0.05) or in combination with Ki67 (p=0.01) and CD38 (p=0.05)] and HLA-DR (p=0.01) than their HIV-unexposed counterparts. Plasma concentrations of IL-2 (p=0.02), IFN-γ (p=0.05) and GM-CSF (p=0.006, stayed sig. after adjustment for multiple comparisons) were significantly lower in HIV- exposed compared to HIV- unexposed individuals.

Conclusions: This study suggests that HIV-exposed individuals from SA have an immune quiescent phenotype, with lower frequencies of activated CCR5-expressing T-cells and CCR5 density per T cell, than their HIV- unexposed counterparts. Since CCR5 expressing T-cells, especially activated ones, are the preferred targets for HIV infection, this study in HIV-discordant couples suggests that CCR5 agonists may be useful to block HIV infection.

No conflict of interest

Abstract: 24

Biomedical Approaches of HIV prevention of transmission

The role of cervical mucus and mucins in HIV/AIDS

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Introduction: Sexual intercourse is the major route of human immunodeficiency virus (HIV) transmission. Our laboratory reported that purified cervical mucins from HIV negative women inhibited HIV-1, whilst the crude cervical mucus did not (Habte *et al.* 2008b). The anti-HIV-1 activity of crude cervical mucus and purified mucins from HIV positive women is unknown. We aimed to compare the anti-HIV-1 activities of the crude cervical mucus and purified mucins from HIV negative and HIV positive women in a large cohort.

Methods: We collected cervical mucus plugs in guanidinium hydrochloride from fifteen HIV negative and eight HIV positive pregnant

women just before delivery, and stirred them overnight to solubilise. We subjected the samples to a low speed centrifugation to remove insoluble material and prepare crude cervical mucus. To purify mucins, we centrifuged samples twice by caesium chloride density gradient ultra-centrifugation, dialyzed against distilled water to desalt and freeze-dried to remove water. We confirmed the purity of mucins by SDS-PAGE and detected mucins by Western blot. We incubated—separately—the crude cervical mucus and purified mucins with HIV-1 for 48 hours, transferred each mixture to TZM-bl cells and detected the HIV-1 neutralization by illuminometer.

Results: The mucin purification profiles showed that caesium chloride density gradient ultra-centrifugation removed protein contaminants from the mucins, as confirmed by the faint protein background on the SDS-PAGE. We detected MUC5AC and MUC5B in all samples using Western blot. We found that the crude cervical mucus and purified mucins from HIV negative and HIV positive women inhibited HIV-1 in an *in vitro* assay, with inter-individual variation among patients from both groups.

Conclusion: Our findings suggest that HIV infection does not compromise the expression of the cervical mucins, and both crude cervical mucus and purified mucins can neutralize HIV-1 in an *in vitro* assay regardless of the HIV status of the participants. We propose that the cervical mucins are promising anti-HIV-1 molecules to be incorporated in the synthesis of a vaginal microbicide.

No conflict of interest

Abstract: 25

Epidemiology of HIV Transmission

Sexual behaviour and condom use as a protection against sexually transmitted infections in student population

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Introduction: The aim of the study was to determine the differences in sexual behaviour and condom use as a protection against sexually transmitted infections (STI) between the first-year and the last-year students.

Materials & Methods: Data were collected by filling anonymous and consented questionnaire in June of 2011 at University of Josip Juraj Strossmayer in Osijek, Croatia.

Results: Out of 857 students in the planned sample, 462 (53.9%) filled out the questionnaire, and 353/462 (76.4%) were sexually active. Data from sexually active students were processed and statistically significant results between first-year and the last-year students were presented. Studied sample consisted of 192/353 (54.4%) first-year students and 161/353 (45.6%) last-year students. Average age of sexual initiation for the first-year students was 17.28±1.29 years, a for the last-year students 18.45±2.14 years, and the difference is significant (Man-Whitney test=10335.00, $p<0.01$). First-year students have lower number of sexual partners ($c^2=28.005$, $p<0.01$), during relationship they had lower number of intercourses with the third person ($c^2=17.947$, $p<0.01$), and feel that lower number of their friends were already sexually active at the time of their own sexual initiation ($c^2=18.350$, $p<0.01$). First-year students more often inform their partners about existing or previous STI ($c^2=14.476$, $p<0.01$) and curiosity significantly influenced their decision regarding sexual initiation ($c^2=8.689$, $p<0.05$). First-year students more often used condom at their first sexual intercourse ($c^2=7.275$, $p<0.01$), and more rarely used withdrawal ($c^2=6.380$, $p<0.05$). At their last sexual intercourse, first-year students more often used any kind of protection ($c^2=3.853$, $p<0.05$),more often used condom ($c^2=11.110$, $p<0.01$) and withdrawal ($c^2=5.156$, $p<0.05$), and more rarely used contraceptive pills ($c^2=4.405$, $p<0.05$). First-year students more often use condom in a permanent relationship ($c^2=13.384$, $p<0.05$), and also plan to use it during following intercourse in the permanent relationship ($c^2=17.575$, $p<0.01$).

Conclusions: Growing condom use and decreasing risky sexual behaviour among students, as well as other adolescents and young adults needs to be maintained. Youth

should learn before sexual initiation that only correct condom use at every sexual intercourse protects them against STI and human immunodeficiency virus (HIV). Sexual education and STI/HIV prevention programmes, positive role of media (television) and civil organisations that communicate with the youth can help that. Such changes among adolescents and young adults should have to be seen in student population as well.

No conflict of interest

Abstract: 26

Epidemiology of HIV Transmission

Phylodynamic analysis of HIV-1 subtype B population in Japan: Identification of large transmission clusters and their network structure

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Introduction: To better understand the epidemiology of HIV-1 subtype B transmission in Japan, we conducted a phylodynamic analysis of viral *pol* sequences from individuals newly diagnosed as HIV-1 seropositive.

Materials & Methods: The study sample comprised cases newly diagnosed as HIV-1 infected and registered in the Japanese Drug Resistance HIV-1 Surveillance Network between 2002 and 2012. Serum samples collected from cases were analyzed for viral protease-reverse transcriptase sequences and their subtypes were determined using phylogenetic-based subtyping. Subsequently, subtype B sequences were selected and their phylogenetic relationships were inferred by three different methods: distance-matrix based, maximum likelihood and Bayesian Markov chain Monte Carlo (MCMC). Transmission clusters were identified based on the following criteria: >95% in interior branch test, >95% in Bayesian posterior probability and <10% in depth-first searches for sub-tree partitions. Chronological phylogeny and time of the most recent common ancestor (tMRCA) of the transmission clusters were estimated by Bayesian MCMC analysis. The structure of the transmission network was estimated using the method proposed by SJ Little et al., 2014.

Results: Of 5018 cases collected between 2002 and 2012, 4398 (87.6%) cases were classified as subtype B. The majority of patients with subtype B were Japanese men who have sex with men (MSM). In the subtype B phylogeny we found over 250 clusters. Two-thirds were small clusters with <10 individuals, and the largest cluster consisted of more than 300 individuals. The majority of cases involved in these clusters were men with MSM behavior as their risk factor. Although a few clusters showed tMRCA in the 1980s, most clusters had tMRCA between 1990 and 2000, suggesting that subtype B infection expanded between MSM in the second half of the 1990s. Based on sample collection areas, most clusters appeared to associate with specific geographic regions. Furthermore, in some large clusters with >9 individuals, their neighboring regions were also involved, suggesting that the network had expanded at a certain developmental stage of transmissions. Some clusters involved non-Japanese HIV strains registered in the Los Alamos database, suggesting that international MSM communities influence the epidemic of subtype B in Japan.

Conclusions: Subtype B transmission clusters expanded rapidly in the last two decades in Japan. While some transmission networks have grown to include individuals from other countries, the majority of networks were limited to particular geographic regions within Japan. Although the international networks are a greater concern for further outbreaks and emergence of novel recombinant variants among MSM, the local networks could be easier to access and control or prevent further transmission.

No conflict of interest

Abstract: 27

Modeling of HIV Transmission

The role of semen on vaginal HIV-1 transmission and on the efficacy of Maraviroc as a topically applied microbicide

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Introduction: All mucosal exposures to HIV occur in the presence of semen. Currently, there is no consensus on the effect of semen on HIV transmission or on the potential effectiveness of topical microbicides. Here, we use an *in vivo* animal model of mucosal HIV transmission to establish the effect of semen on vaginal HIV infection and on the efficacy of topical microbicides.

Methods: We utilized bone marrow/liver/Thymus (BLT) humanized mice; a model validated for the study of vaginal HIV transmission and HIV prevention strategies. We first evaluated the transmission of transmitted/founder viruses in the presence or absence of human semen. In addition, we also evaluated the effect of semen on cell-associated HIV transmission. Lastly, we evaluated the efficacy of topically applied microbicides in the presence of semen using the CCR5 antagonist, maraviroc. Log rank Mantel-Cox was used to analyze the data.

Results: To determine the effect of semen on vaginal transmission of HIV-1_{CH040}, a transmitted founder (T/F) virus, was resuspended in human semen and vaginally administered to BLT mice. Efficient transmission was observed regardless of the presence (6/6) or absence (4/4) of semen. No differences were noted in the levels of peripheral viral load or CD4+ T cell decline between the two groups. When cell-associated HIV was used for challenge in the presence of semen, 3/4 BLT mice became infected compared to 4/4 in the control arm. When animals were treated vaginally with maraviroc and then challenged with HIV in semen, complete protection was observed (6/6).

Conclusions: Our results demonstrate that semen does not enhance transmission of either cell-free or cell-associated HIV. In addition, semen does not diminish the protective effect of maraviroc from vaginal HIV infection when applied topically. Our results establish a new paradigm for the evaluation of HIV prevention strategies that includes human semen in the context of cell-free and cell-associated virus.

No conflict of interest

Abstract: 28

Modeling of HIV Transmission

Modeling the impact of targeting treatment and prevention to the migrant population of male miners in a generalized epidemic setting

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Introduction: Migrant populations are thought to have played a significant role in the initial spread of HIV in sub-Saharan Africa. Miners in particular have been identified as a key driver of the HIV epidemic in South Africa due to their circular migration patterns and elevated risk behaviors. We used a computer model to quantify the potential impact of targeting treatment and prevention to male miners.

Materials & Methods: We augmented an individual-based network model, EMOD-HIV *v0.8*, to include a migrant population representative of South African miners. Simulated miners routinely migrate between their home community and a mining community, where an external incidence source replaces sexual transmission.

Results: Targeting miners with treatment, perfect prevention, or combination treatment and prevention averted 2.7, 203.3, and 219.8 thousand infections over a 20-year period with 3% discounting, respectively. These results

come from baseline assumptions that 5% of the male population engages in mining and that each miner visits home monthly for one week. In comparison, universal test and treat resulted in 3.8 million discounted infections averted over the same time period. We increased the frequency of home visits, however the impact changed only marginally. We then exaggerated the size of the male mining population to 20%, resulting in 62.5, 890.6, and 938.2 thousand discounted infections averted from treatment, prevention, and combination intervention. Finally, we changed the timing of the prevention intervention from 2015 back to 1985 in 1-year increments. To halve the incidence rate in 2020, prevention needed to start in 1989. Result may underestimate impact by not modeling transmission at the mine.

Conclusion: While targeting miners can be cost effective, here we see that these interventions will have a modest impact on the overall incidence in a generalized epidemic. Nonetheless, targeting migrants remains a promising tool for mitigating the future burden of HIV in low-level and concentrated epidemics.

Conflict of interest: This work was supported by Bill and Melinda Gates through the Global Good Fund at Intellectual Ventures Laboratory. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the work.

Abstract: 29

Mother to Child Transmission

Effectiveness of the protocol for the Prevention of Mother to Child Transmission of HIV applied at Saint Camille Medical Centre in Ouagadougou, Burkina Faso

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Background: Despite many prevention efforts, the number of children infected by HIV in sub-Saharan Africa through vertical transmission remains high. This infection can be reduced through programs of prevention of mother to child HIV transmission (PMTCT). The objective in this study was to evaluate the effectiveness of the PMTCT protocol at Saint Camille Medical Centre in Ouagadougou, Burkina Faso.

Methods: From August 2012 to September 2013, samples of dried blood spot (DBS) were collected from 160 children aged 6 weeks born from HIV-1 positive mothers who were under PMTCT protocol at Saint Camille Medical Centre and 40 children of the same age group from orphanages and whose mothers were dead or unknown. The samples were tested using the Abbott Real Time HIV-1 Qualitative kit. The clinical data of mothers were collected and analyzed using SPSS Version 17.0 and Epi Info Version 6.0 softwares.

Results: Among pregnant women in this study, 52.5% were predominantly young (24-29 years) and 60.62% were housewives. In total, 50.5 % (101/200) were in combination AZT/3TC/NVP and 29.5 % (59 /200) were on prophylaxis (AZT/3TC). The rate of vertical transmission of HIV- 1 was 0.0 % ($p < 0.001$) in children whose mothers were taking a combination of AZT/3TC/NVP (0/ 101) or were on a prophylaxis AZT/3TC treatment (0 /59). While, the rate of HIV-1 transmission in orphaned children was of 15.0 % (6 /40).

Conclusion: The PMTCT protocol is effective and reduces very significantly ($p < 0.001$) the risk of transmission of HIV- 1 from mother to child. In addition, screening by PCR of orphaned children vertically infected with HIV, enabled them to receive an early treatment.

No conflict of interest

Abstract: 30

Mother to Child Transmission

Male partner antenatal clinical attendance is associated with improved infant HIV-free survival

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Introduction: Male involvement in PMTCT in sub-Saharan Africa is recommended however evidence supporting improved outcomes with participation is limited. This prospective cohort study investigate the relationship between male involvement in ANC based PMTCT services and infant HIV-free-survival.

Materials & Methods: From 2009 to 2013, HIV-infected pregnant women were enrolled from six clinics in Nairobi, Kenya and followed with their infants until six weeks post-partum as part of a study evaluating perinatal breastfeeding counseling. Women were screened for consent for partner involvement. If females consented, men were encouraged to attend through female requests and formal invitation letters. Standardized questionnaires were used to survey all enrolled participants. Males who failed to attend antenatally had questionnaires provided for self-completion and return by the enrolled female. Data on sociodemographics, HIV testing, ANC attendance, HIV knowledge and partner PMTCT discussions were collected. Informed consent was obtained from all subjects.

Results: Among 830 enrolled women, 519 (62.5%) consented to male participation and 136 (26.2%) partners attended the ANC. For the 383 (73.8%) women whose partners failed to attend, 63 (16.4%) were surveyed via outreach. Partner attendance was more likely among couples in monogamous relationships who had previously discussed PMTCT interventions and among men who reported prior HIV testing, being aware that vertical transmission was possible and that their female partner was HIV-positive. In multivariate analysis only male report of prior HIV testing remained significantly associated with ANC attendance (aOR=3.7; 95%CI:1.5-8.9, p=0.003). By six weeks postpartum 33 (6.6%) of 499 infants acquired HIV or died. Infants born to women with male attendance had an incidence of vertical transmission or death of 20.2/100 person-years (95% CI: 6.5-62.6), whereas those born to mothers without partner attendance had an incidence of 76.4/100 person-years (95% CI: 53.4-109.2). HIV-free-survival was 3.7-fold higher among infants of women whose partners attended the ANC (HR=3.7 95%CI:1.1-12.1, p=0.03). Adjusting for maternal and infant ARV use and clinic infant HIV-free-survival remained significantly greater among those born to females with male participation (aHR=3.6 95%CI:1.1-11.7, p=0.03).

Conclusions: Male ANC attendance was greater among those previously exposed to HIV testing and partner involvement was associated with improved infant HIV-free-survival in this prospective study. Promotion of male activity in the ANC setting may serve to improve infant outcomes and should be evaluated in further in alternative settings.

No conflict of interest

Abstract: 31

Transmission of HIV Drug Resistance

HIV-1 genotyping and antiretroviral drug-resistance mutations determination among drug naive individuals infected in Morocco

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Introduction: The human immunodeficiency virus (HIV-1) is the causative agent of AIDS and one of the most devastating pandemics in human. At the end of 2012, a total of 35.3 million people were living with HIV-1 and around 2.3 million people were newly infected. The first AIDS case in Morocco was identified in 1986, and despite the low initial prevalence of HIV-1, a program to fight AIDS was established and allowed an early introduction of HAART in Morocco. Despite significant progress in HIV-1 prevention and treatment, the emergence of viral resistant strains remains a major problem for the medical management of HIV-1 infected individuals.

Objectives: The aims of the present study was to determine viral subtypes and antiretroviral resistance-associated mutations in HIV-1 infected, treatment-naive individuals in Morocco during the period 2011-2014.

Methods: Both protease (PROT) and reverse transcriptase (RT) genes from 215 subjects were sequenced and analysis for resistance-associated mutations to NRTIs, NNRTIs, and PIs. Genotypic resistance was interpreted according to Stanford and ANRS algorithms. Phylogenetic analysis was performed by the Neighbor Joining method. Bootstrap analysis was performed to generate 1000 replications.

Results: Among 215 subjects, we identified sixteen subtypes and CRFs with frequencies ranging from 0,5% to 39,1%: B(39,1%), CRF-02_AG(35.3%), CRF-07_BC(4,2%), CRF-36_cpx(4.2%), D(3,7%), CRF-18_cpx(3,3%), CRF-45_cpx(2,3%), CRF-01A1(1,9%) F2(1,4%), G(0.9%), CRF-05_DF(0.9%), CRF-19_cpx(0.9%), CRF-05_DF(0.5%), CRF-07_BC(0.5%), CRF-BF(0.5%), CRF-BG(0,5%). These results showed that non-B subtypes become more prevalent than B subtypes (61% vs 39%) although B subtypes remains the predominant circulating strains. The most predominant non-B subtype was CRF02_AG (57% of non-B subtypes). The phylogenetic analysis of PROT region identified two major clusters. One included strains grouped together with morocan reference sequences to constitute a country-specific group. The second cluster included strains clustered with reference sequences from West Africa and Europe. Several minor mutations have been identified in PROT region. The combination of those minor mutations was associated with resistance to some antiretroviral drugs. Two major mutations were also identified: I84V and I54M. No resistance mutations were detected in the RT analyzed region.

Conclusions: Our results revealed a large dissemination of HIV-1 non-B subtypes in our population, as well as the emergence of minor and major mutations among treatment-naïve individuals. These results highlight the importance of HIV-1 molecular epidemiology surveillance in Morocco.

No conflict of interest

Abstract: 32

Transmission of HIV Drug Resistance

Long-term risk of HIV drug resistance after PrEP breakthrough infection: Implications from a mathematical model of the HIV latent reservoir

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Background: Clinical trials of HIV pre-exposure prophylaxis (PrEP) have found little risk of HIV drug resistance after breakthrough infection, provided that the infection is detected and PrEP is discontinued in a timely manner. However, broad roll-out of PrEP in resource-limited settings cannot guarantee ideal monitoring for all patients. Also unknown is the transmissibility of PrEP-related drug resistance, which may differ from that of ART-related drug resistance due to transmitted founder virus dynamics.

Methods: We developed a mathematical model that links PrEP adherence to the dynamic populations of drug-sensitive and drug-resistant virus, distinguishing between replicating virus and the long-lived latent

reservoir. The model was parameterized for tenofovir-based oral PrEP with viral fitness and resistance pattern data for *K65R*. Novel model structures were explored to study transmitter founder virus dynamics.
Results: The size and persistence of the modeled drug-resistant viral pool grew fastest during acute viremia, but continued to grow over the duration of undetected infection. After cessation of oral PrEP, the latent HIV reservoir harbored approximately double the proportion of *K65R* compared to the actively replicating pool. Host immunity, which influences viral load setpoint, modulated the proportion of *K65R* over an order of magnitude, as did patterns of adherence during PrEP use. Resistance acquired during early HIV infection could potentially elevate the transmissibility of resistance, which was seen when models assumed early establishment of a stable founder virus.

Conclusions: The need for early detection of breakthrough infections during PrEP is expected to be highly heterogeneous, with the greatest need among patients with pre-existing immune impairment. Importance of adherence-driven pharmacokinetics implies that other PrEP methods, such as microbicides, may yield very different resistance patterns. More research is needed to understand transmissibility of drug resistance acquired during PrEP.

No conflict of interest

Abstract: 33

Virology of HIV Transmission

Protective HLA alleles reduce markers of gut damage and microbial translocation and preserve the cellular immune response during acute HIV-1 infection

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Introduction: Efforts to elucidate protective host factors in HIV-1 infection often rely on cross-sectional data to determine factors influencing pathogenesis. Here, we study a cohort of 127 acutely infected Zambians with longitudinal CD4 counts up to 5 years post infection to identify novel HLA alleles associated with disease progression.

Materials & Methods: Cox proportional hazard models were used to elucidate protective and deleterious HLA alleles. Plasma cytokines were measured at seroconversion (median 45 days post infection), 3, and 6 months post infection using the Luminex platform. Multicolor flow cytometry was used to assess cellular activation.

Results: In a multivariable Cox model, HLA-B*1401, B*57, B*5801, B*81, DQB1*02, and DRB1*15 were found to provide significant protection from CD4 T cell decline. Protective HLA class I alleles were associated with significantly lower plasma lipopolysaccharide (LPS) levels and fewer activated (CD38+, PD-1+) CD8+ T cells early in acute infection, a time point before these protective alleles significantly altered plasma viral load (VL). Furthermore, protective HLA class I alleles were associated with a decrease in IL-10 levels over time and lower levels of iFABP in plasma at 6 months post infection. This data suggests that protective cellular immune responses operate early in acute infection before control of plasma VL is detected.

Conclusions: This study of a well-characterized subtype C Zambian cohort of acutely infected individuals provides an opportunity to elucidate host immunogenetic factors contributing to HIV-1 pathogenesis and to investigate the underlying immunological mechanisms. This data suggests that protective HLA alleles can influence disease

course early in acute infection by maintaining gut integrity, limiting microbial translocation, and ultimately preserving functional cellular immune responses by reducing inflammation.

No conflict of interest

Abstract: 34

Virology of HIV Transmission

In-vitro fitness of HIV-1 transmitted/founder versus non-transmitted full-length genome infectious molecular clones

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Introduction: In ~80% of heterosexual transmissions of HIV-1, an infected individual with a diverse viral quasispecies transmits a single viral variant, the Transmitted/Founder (TF), to a naïve host. Evidence is building that TF variants are enriched for certain genetic and phenotypic characteristics that presumably enhance the efficiency of transmission. However, the mechanisms involved are largely ambiguous, partially because studies using full-length genomes in transmission pairs are lacking.

Materials & Methods: We have performed HIV near full-length (NFL) single genome amplification from six subtype C acutely infected individuals and each of their chronically infected virologically linked partners in the Zambia-Emory HIV Research Project. Phylogenetic analysis performed on the 118 NFL genomes (mean 18/transmission pair) confirms epidemiologically linked transmission as well as infection by a single viral variant in each case. We have generated 5 TF & 34 non-transmitted (NT) full-length infectious molecular clones from 5 transmission pairs and assayed for particle infectivity by dividing the virus titer on TZM-bl cells by the RT activity of the virus stock.

Results: The particle infectivity of the TF compared to the median of the NT variants for all matched transmission pairs was not statistically significant (p=0.22). However, particle infectivity correlated with the amount of glycosylation on the Env V1-V4 region (R=0.40, p= 0.01) as well as with replication in PBMCs for a subset of tested viruses (R=.823 p=0.01), suggesting that previous findings showing less glycosylation on TF viruses could mean lower replicative capacities *in vitro*. However, preliminary data suggests that lower replicating, less glycosylated viruses, may preferentially productively infect monocyte-derived dendritic cells.

Conclusions: Understanding the characteristics of TF viruses that allow for efficient transmission will aid in prophylaxis and early intervention efforts.

No conflict of interest

Abstract: 35

Virology of HIV Transmission

Characterization of the Dolutegravir (DTG) mutation R263K in combination with classical Raltegravir mutations to explain the absence of resistance to DTG in the clinic

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Introduction: No HIV-infected patient, naive to the therapeutic use of integrase strand transfer inhibitors (INSTIs), has yet developed

resistance against dolutegravir (DTG). We have hypothesized that the outgrowth of DTG-resistant viruses may be unable to occur, based on the strategic location of the R263K mutation that is selected by DTG within the integrase enzyme. To further characterize the resistance profile of DTG, we selected for resistance in tissue culture against this compound, and combined the R263K mutation together with mutations that are associated with resistance to other members of the INSTI family of drugs.

Materials and methods: We assessed the activity of purified recombinant integrase biochemically and the infectivity of NL4.3 virus in tissue culture, both harbouring R263K and other resistance mutations of relevance.

Results: R263K was the most frequent integrase resistance mutation to arise in subtype B. R263K alone conferred an approximate 2-5-fold level of resistance to DTG and a 30% drop in levels of recombinant integrase strand transfer activity and viral replicative capacity. Over > 4 years, no compensatory mutations were identified. To investigate cross resistance to first generation INSTIs, we combined R263K with four classical INSTI resistance mutations that are associated with resistance against raltegravir (RAL) and elvitegravir (EVG): E92Q, Y143R, Q148R, and N155H. Biochemically, each combination reduced the strand transfer activity of recombinant integrase and only $IN_{Q148R/R263K}$ had increased resistance to DTG. The $NL4.3_{IN(Y143R/R263K)}$ and -$NL4.3_{IN(Q148R/R263K)}$ viruses grew very poorly, however the $NL4.3_{IN(N155H/R263K)}$ combination partially restored the infectious defect of the R263K mutant, while further increasing DTG resistance by ~ 1.7 fold.

Conclusions: These results stand in contrast to those obtained with other drugs, whereby secondary mutations increase overall levels of drug resistance and simultaneously increase viral replication and enzyme function, and help to explain why primary resistance to DTG has not yet arisen in clinical studies. Although the combination of N155H + R263K, represents a possible mechanism through which resistance might develop, this combination was identified only after DTG selection with $NL4.3_{IN(N155H)}$ as the starting genotype, and was also recently identified in a first generation INSTI-experienced patient. However, the selection of these mutations appears to be directional because R263K-containing HIV-1 has yet to select for N155H *in vitro* or *in vivo.* Further investigation is needed to determine whether this combination is clinically relevant with respect to DTG. Expanding these experiments to an animal model would help to address this question and research in our laboratory has shown that the same mutations that confer resistance to INSTIs in HIV also do so in SIV. Our findings establish that resistance against RAL vs DTG in first-line can only occur via mutually exclusive mutational pathways and explain why the outgrowth of DTG resistant variants may be unlikely to occur, even after selection of the R263K substitution.

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Abstract: 36

Virology of HIV Transmission

Changes in viral population kinetics following HIV-1 superinfection

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Introduction: Elucidation of factors influencing HIV superinfection with a second viral strain, despite pre-existing immune responses to the primary infecting strain, may provide insights into correlates of protection. Superinfection is frequently associated with a spike in viral load which could be due to loss of control of the primary infecting virus, or the superinfecting virus, or both. To evaluate if pre-existing responses to primary infection differentially controlled viral populations following superinfection, we estimated viral population kinetics at time points before and after superinfection.

Material & Methods: We performed 454 deep sequencing of two genomic regions, *gag* p17 (332bp) and *env* C2C3 (403bp), on three participants who were known to be

superinfected. To enable quantification of the input cDNA, and control for PCR and sequencing errors, the cDNA was labelled with a unique primer ID.

Results: In all three participants the temporary increase in viral load associated with superinfection was predominantly due to the superinfecting viral strain, which became the major circulating variant in two of the three participants. Within the regions examined, we did not detect recombination in the *gag* region, however in one of three participants recombination was found within the *env* C2C3 region in ~20% of viral sequences 15 weeks after superinfection.

Conclusions: The superinfecting virus was not controlled following infection within two participants, suggesting that responses elicited to the primary strain were not cross-protective against the second strain at the time of superinfection. In one participant however, there was subsequent control of the superinfecting strain following its introduction, this could be indicative of a broader CTL (Cytotoxic T Lymphocyte) response and warrants further investigation.

No conflict of interest

Abstract: 37

Virology of HIV Transmission

Maraviroc induces HIV production, potentially via the NF-kB pathway

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Background: Recent clinical data from maraviroc intensification trials indicated that addition of maraviroc to combination antiretroviral therapy (cART) may increase immune activation. Furthermore, an increase in CD69, a cellular activation marker, was observed when peripheral $CD4^+$ T-cells from healthy individuals and HIV-infected patients were cultured in the presence of maraviroc. The objective of the current study is to investigate maraviroc induced cell activation and HIV production both *in vivo* during a randomised maraviroc intensification trial and *in vitro* in donor peripheral blood mononuclear cells (PBMCs).

Methods: Using ultra-sensitive droplet digital PCR (ddPCR) we performed a detailed longitudinal virological and immunological analysis in 15 immune non-responders who participated in a 48-week, double-blind, placebo-controlled maraviroc intensification trial. We assessed changes in total HIV DNA and 2-LTR circles, per million PBMCs. We also analyzed the relative changes of HIV RNA expression and NF-κB regulated genes (TNF-a, IFN-y, IL-10 and IL-6). Furthermore, we examined the expression of CCR5 ligands and immune activation markers (IL-2R, IP-10, sICAM and TWEAK) in plasma by Luminex. To investigate the effect of maraviroc on HIV production, we infected healthy donor derived PBMCs with an X4-tropic reference strain (HXB2) in the absence or presence of increasing levels of maraviroc. After seven days of infection, viral production was assessed in culture supernatant by analysis of CA-p24.

Results: Patient characteristics and immunological and virological baseline values did not differ between the maraviroc intensification and placebo group. No difference in total HIV DNA and 2-LTR circles was observed. During the first eight weeks of maraviroc intensification, a significant difference in relative HIV RNA expression was detected. In the maraviroc group (n=10), a slight increase in relative HIV RNA expression was seen as compared to a decrease in the placebo group (n=5) (maraviroc increase 1.7 fold; placebo decrease 4.2 fold; p=0.03). After eight weeks we also measured a 2.3 fold increase in plasma CCR5 ligand MIP-1β in the maraviroc group. During this period, a significant difference in NF-kB regulated gene expression (IFN-y, IL-6) was observed increasing the maraviroc group and decreasing

in the placebo group (IFN-y p=0.02; IL-6 p=0.03). Addition of maraviroc to effective cART did not result in a different expression pattern of the activation markers in plasma as compared to placebo. *In vitro* assays demonstrated a significant dose-dependent increase in HIV production (HXB2 CA-p24) when maraviroc was added to PBMCs (2.2 fold). This significant increase in virus production was observed in all experiments (n=9) and at all dosages used (ranging from 1pM – 1µM).

Conclusions: Maraviroc intensification of cART in immunological non-responders slightly increases CCR5-ligand expression, NF-κB regulated gene expression and HIV RNA expression. These patient derived data are in line with our *in vitro* observation of maraviroc induced HIV production. Together, these data indicate that maraviroc induces HIV production, potentially via upregulation of the NF-kB pathway. This study warrants further investigation into the potential consequences of this observation for the use of maraviroc as a prophylaxis or anti-latency antiretroviral drug.

No conflict of interest

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Principles of Intervention

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