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Abstract Book

8th International Workshop on HIV Transmission

4 - 5 October 2013, Barcelona, Spain

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Abstracts

Abstract: 01

Virology of HIV Transmission

Virologic and clinical correlates of genetic selection bias at the transmission bottleneck

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Background: HIV infection occurs by the transmission of one or a few of the virions present in the donor. This process is poorly understood and it is not known if this transmission bottleneck is mediated by an active selection process that induces a bias for certain genetic variants or is the consequence of a stochastically unbiased event.

Methods: We propose a logistic regression model of transmission selection bias that assumes the probability of transmitting a particular viral variant is related to the relative frequency of that variant in the quasispecies and the intrinsic infection advantage of that variant relative to all others. Under this model, selection at the transmission bottleneck is unbiased if no variant has a relative advantage. We tested this model on 123 epidemiologically linked Zambian transmission couples, for whom Gag/Pol/Nef bulk sequences were available for both donor and recipient soon after transmission (median 45d). We grouped viruses into binary groups based on the presence or absence of the donor majority residue at each site, then classified each variant as transmitted if it was observed in the recipient. We then tested virologic and clinical factors as correlates of odds of transmission.

Results: A majority (99.3%) of the 213551 non-mixture (>75% population sequence peak height) residues in the donors were transmitted, reflecting the dominant role that relative quasispecies frequency plays in selection of the founder virus. Overall sequence diversity reduced the probability of transmission ($p<1e-6$). Notably, the log-odds of transmission was correlated with the relative frequency of the residue in the overall cohort (rarest residues transmitted at 87% frequency, $p<1e-100$). Similarly, residues with a large effect on *in silico* protein stability ($p<5e-3$), those with a high number of putative compensatory mutations ($p<5e-7$), and those from partners with high transmitted/founder *gag in vitro* replicative capacity ($p<5e-7$) had higher odds of transmission. Taken together, these results suggest a selection bias for viruses that are closer to consensus and are putatively more fit. As predicted by our model, well-established risk factors—donor viral load, male-to-female transmission, and active genitourinary infection in the uninfected partner—each independently reduced the transmission selection bias ($p<1e-4$).
Using the sequence features predicted to induce a selection bias, we defined a 'transmissibility' score. This score significantly distinguished chronically infected individuals who had transmitted from those who had not (N=179), independent of other risk factors ($p=0.01$), suggesting that individuals whose dominant variants are predicted to face a steep selection bias are less likely to transmit the virus.

Conclusion: The identification of virologic parameters that strongly correlate with transmission of donor polymorphisms argues for biased selection of virions, while our ability to use these parameters to predict whether an individual would transmit suggests the clinical importance of this transmission selection bias. That this bias is reduced by well-characterized risk factors is consistent with these risk factors increasing the overall ability of any virion to establish infection and suggests that behavioral or therapeutic reduction of risk will increase the relative bias induced by the genetic bottleneck.

Financial relationship(s): JMC and DH are employees and shareholders of Microsoft Corp.

Abstract: 02

Biology of HIV Transmission

Intestinal myeloid DCs display an activated phenotype and are less susceptible to HIV-1 infection compared to blood DCs.

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Introduction: We recently showed that human colonic lamina propria (LP) CD11c+ DC actively shuttle R5 HIV-1 across an intact epithelial barrier and transfer infection to CD4+ T cells. However the susceptibility of intestinal DC to HIV infection has been poorly investigated, due to difficulties in isolating mucosal DC.

Material & Methods: CD11c+ myeloid DC obtained from the colonic LP were further characterized as CD103+ and CX3CR1+ and the expression of HIV-1 receptors analyzed in comparison to blood DCs. Supernatant obtained from an *ex vivo* culture of healthy human colonic mucosa was used to condition monocyte-derived DC in an in vitro model as to mimic the exposure of DC to intestinal microenvironment. Conditioned–DC (C-DC) were analyzed by flow cytometry for the expression of HIV-1 receptors and activation markers, and incubated *in vitro* with either R5 or X4 HIV-1 to study their susceptibility to infection.

Results: C-DC displayed an activated phenotype, a significant down-regulation of CCR5, CD4 and CX3CR1, an up-regulation of CXCR4 and a moderate modulation of DC-SIGN expression compared to unconditioned DC. No change in the CD103 expression was observed. Interestingly, both R5 and X4 HIV-1 replicated less efficiently in C-DC compared to unconditioned DC. Colonic supernatants contained the CCR5-binding chemokines Mip1b and MCP-1 and the CX3CR1 ligand fractalkine, whereas the CXCR4 ligand SDF-1a was absent. IL-10 and IL-2, described to induce CXCR4 up-regulation on DC, were also detected. Thus, this specific intestinal milieu may determine the observed phenotype.

Conclusions: Both CX3CR1+ and CD103+ CD11c+ DCs were detected in human colonic LP. Interestingly CD11c+ DC showed lower CCR5 and higher CXCR4 expression compared to blood DC, and a similar activation profile, which confirmed the results obtained after intestinal conditioning. Thus, the intestinal microenvironment module the expression of HIV receptors on DCs and their capability to replicate the virus.

No conflict of interest

Abstract: 03

Biology of HIV Transmission

DC-SIGNR polymorphism and expression: correlation with dendritic cell count and subsets in Indian HIV-1 infected patients and injecting drug users

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Introduction DC-SIGNR is a C-type lectin receptor and interacts with a plethora of pathogens including HIV-1. DC-SIGNR is proposed to play a vital role in binding to HIV-1 gp120 thereby facilitating transmission of HIV to CD4+ T cell targets.

Objective To quantitate the dendritic cell and its subset and study the expression of DC-SIGNR on PBMCs and its polymorphic variants.

Methodology Blood from 230 seronegative healthy individuals, 200 injecting drug users, and 230 patients infected with HIV-1 was collected. The repeat region polymorphism in DC-SIGNR was performed by PCR. Peripheral blood DC and their subset frequency was determined by flow cytometry. DC-SIGNR expression on PBMCs was determined by real time PCR and flow cytometry in HIV-1 antiretroviral naïve patients and healthy individuals and in culture of monocyte derived dendritic cells from healthy individuals.

Results The frequency of homozygous *DC-SIGNR* 7/7 genotype and allele 7 was significantly higher in patients infected with HIV-1 whereas frequency of heterozygous *DC-SIGNR* 7/5 genotype and allele 5 was significantly higher in injecting drug users. A salient finding of this study was the association of the heterozygous 7/5 *DC-SIGNR* genotypes with higher percentage of DC and their subsets and higher CD4+ T cell counts and lower viral load compared to the homozygous 7/7 *DC-SIGNR* genotypes in patients infected with HIV-1. The expression of DC-SIGNR was higher in patients infected with HIV-1 with positive correlation with CD4+ T cells as compared to healthy individuals. Dendritic cells in culture, on infecting with HIV-1 virus (AIIMS 53), showed up regulation of DC-SIGNR and Co-stimulatory molecules.

Conclusions: This is the first study to assess the DC subsets, and its association with DC-SIGNR polymorphism in injecting drug users and HIV-1 infected patients and DC-SIGNR expression in HIV-1 infected patients. This study suggests the protective role of 7/5 *DC-SIGNR* genotype in HIV-1 infection and the higher expression of DC-SIGNR in HIV-1 infection suggest possible role DC-SIGNR in activated dendritic cells during HIV-1 infection and needs to be studied.

No conflict of interest

Abstract: 05

Biomedical Approaches of HIV prevention of transmission

The epitopes of the HIV-1 neutralizing llama vhhs 1B5 and L81H9 overlap with the gp120 co-receptor binding site

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Introduction: The entry process of HIV-1 is mediated by binding of the gp120 subunit of the viral envelope protein to the cellular CD4 receptor followed by binding to the co-receptor. Drugs that interfere with this process by binding to the highly conserved CD4 binding site or co-receptor binding site may be useful to prevent HIV-1 infection. Recently, several potent, broadly HIV-1 neutralizing llama heavy-chain only antibody fragments (VHHs) directed towards gp120 have been described. In this study, we mapped the putative epitopes of the VHHs 1B5 and L81H9 on gp120.

Methods and Results: Dose escalation studies with 1B5 yielded two 1B5 resistant viruses, each having three mutations in gp120. The mutants were cross-resistant to L81H9, but also to several other entry inhibitors, such as the VHH A12 that targets the CD4 binding site and hardly competes with 1B5 or L81H9 binding. Furthermore, we showed that the 1B5 resistant viruses had reduced viral replication capacity in primary macrophages. By site-directed mutagenesis in non-isogenic envelopes, two amino acid substitutions, P417L and R419K, were identified to be crucial in resistance towards 1B5, but as expected not towards A12. The epitope for 1B5 and L81H9 was studied in more detail using gp120 alanine scanning. The scans confirmed R419, which is part of the co-receptor binding site, as key residues for both 1B5 and L81H9.

Conclusion: The neutralization capacity of 1B5 and L81H9 are most likely due to the fact that they block the co-receptor binding site.

No conflict of interest

Abstract: 06

Epidemiology of HIV Transmission

Nationwide HIV-1 transmission dynamics estimated by molecular evolutionary analysis in Japan

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Background: To clarify HIV transmission dynamics from a large collection of viral sequences, a useful tool is phylodynamic analysis. We used this tool to analyze HIV *pol* sequence data from our nationwide surveillance network to reveal the dynamics of HIV transmission in Japan.

Material & Methods: Nucleotide sequences of the protease-reverse transcriptase (RT) gene were obtained from 4393 newly diagnosed HIV patients in 2003-2011. These sequences were then aligned with subtype reference sequences retrieved from the HIV database, and subtypes belonging to each sequence segment were determined using similarity plot analysis against subtype references. Domestic transmission clusters (infection networks) were identified by combined monophyly evaluation using three different phylogenetic methods: neighbor-joining method with interior branch test, maximum likelihood method, and Bayesian Markov chain Monte Carlo (MCMC) method. Chronological phylogeny, median time of the most recent common ancestor (tMRCA), and basic reproductive number (R_0) were also inferred by Bayesian MCMC coalescent analysis using BEAST1.7.4.

Results: The predominant subtypes in Japan (with number of patients and prevalence) were subtype B (*n*=3899: 88.8%) and CRF01_AE (*n*=344: 7.8%). Other minor subtypes were found: C (*n*=46), CRF02_AG (*n*=36), G (*n*=15), F (*n*=9), CRF06_cpx (*n*=3), CRF07_BC (*n*=2), and CRF12_BF (*n*=2), and CRF33_01B (*n*=2). Subtypes D, CRF08_BC and CRF28 or 29_BF were detected in one patient. Another 32 patients had unknown forms of intra-subtype recombinants. Phylodynamic analysis yielded four major findings. 1) Although tMRCAs of a few infection networks of subtype B dated to the 1980s, many had spread between men having sex with men (MSM) from the second half of the 1990s. 2) CRF01_AE was also transmitted into Japan through heterosexual and intravenous drug user routes in the 1990s. 3) In the 1990s, minor subtypes and recombinant viruses also colonized in some groups that mingled with foreigners. 4) In the 2000s, CRF01_AE was also transmitted to MSM communities and might have generated some domestically circulated recombinants between subtypes 01_AE and B. R_0 of subtypes B, C, F and CRF01_AE in Japan (3.3, 3.2, 2.1, and 3.7, respectively) did not differ significantly, but the R_0s of subtypes G and CRF02_AG (7.7 and 6.9) were significantly higher than those of other subtypes.

Conclusions: These results suggest that intra-subtype recombinants and a local population network with high infectivity may become concerns, although MSM is still the main risk behavior of HIV-1 transmission in Japan.

Financial relationship(s): This work was supported by a Grant-in-Aid for AIDS research from the Ministry of Health, Labour, and Welfare of Japan [H22-AIDS-004].

Abstract: 07

Biology of HIV Transmission

Host factors, transmitted viral characteristics, and viral adaptation work in concert to define HIV-1 subtype C disease progression.

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Introduction: Efforts to elucidate protective host factors in HIV-1 infection often rely on cross-sectional viral loads (VL) or CD4 T cell counts to determine factors influencing pathogenesis.

Methods: Here, we study a cohort of 127 acutely infected Zambians with longitudinal plasma VL and CD4 counts up to 5 years post infection as a more sensitive method to identify novel host and viral characteristics directly associated with disease progression. Plasma VL and CD4 counts were assessed at 3-month intervals after seroconversion for 127 acutely infected Zambians for up to 5 years. HLA genotyping was performed using genomic DNA and PCR-based techniques. Viral replicative capacity (vRC) was assessed by cloning the *gag* gene from acute time points into MJ4, a subtype C proviral vector, and infecting a CEM T cell line with Gag-MJ4 chimeric viruses. Kaplan-Meier analyses and Cox proportional hazard models with an end-point defined by CD4 counts <300 were used to investigate protective and deleterious HLA class I and II alleles.

Results: HLA-B*1401, B*81, B*57/C*18, DQB1*02, and DRB1*15 were found to provide significant protection from CD4 decline, while HLA-A*03, A*24, and C*17 were deleterious. Moreover, the effects of these alleles were found to be additive, such that individuals with 2 or more protective alleles experienced significantly slower CD4 decline. Meanwhile, sharing HLA-B alleles with a transmitting partner resulted in a significant risk for accelerated CD4 decline, reflecting the impact of pre-transmission viral adaptation on immune control. In multivariable models, HLA-I/II, set point VL, gender, HLA-B sharing and vRC were found to be independent predictors of CD4 decline, as defined by reaching an endpoint of 300 CD4 counts.

Conclusion: This study of a well-characterized cohort of acutely infected individuals provides unique insight into the independent contributions of host immunogenetics, transmitted viral characteristics, and viral adaptation to HIV-1 pathogenesis and will help to elucidate mechanisms of control, which may in turn define correlates of protection.

No conflict of interest

Abstract: 08

Virology of HIV Transmission

Frequency and dynamics of transmitted polymorphisms and their impact on early pathogenesis in heterosexual couples in Zambia

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Background: HIV escapes cellular immune response by selecting mutations that are associated with the HLA alleles carried by an individual. Some escape mutations are known to accumulate in the population, suggesting transmission to HLA-mismatched recipients, but the extent and impact on early pathogenesis of their transmission is poorly understood.

Methods: In a group of 169 epidemiologically-linked transmission pairs from a Zambian cohort, we studied the frequency and transmission of HIV polymorphisms in Gag, Pol and Nef by Sanger sequencing of population PCR amplicons in the transmitting partner and the seroconverter near the time of transmission (median=45.5 days post-infection). Positions associated to HLA-I molecules were identified among a multicohort Southern African sequences dataset using a phylogenetically informed method. Polymorphisms statistically-linked with HLA alleles ('escapes') or located in well-defined CTL epitopes were quantified according to each individual's HLA-I alleles and associated with clinical parameters such as set-point VL and CD4 count on the linked-recipient. Finally, we studied the dynamics of these polymorphisms on longitudinal Gag, Pol and Nef sequences obtained at 6 months intervals for 2 years.

Results: Gag, Pol and Nef proteins of transmitting partners had a large number of polymorphisms (medians of 35.5, 41 and 23, respectively) but only 24.2% of them were associated with the individuals HLA-I alleles (~19% escape and ~11% epitope-located). The majority of polymorphisms (~96%) were transmitted to the epidemiologically-linked partner, with a bias against transmission of donor escapes (91.1%, p=0.0001) and for consensus from donor mixtures (~60% for consensus vs 40% for polymorphisms; p=0.0000000001). Overall, 16.9% of the transmitted polymorphisms were relevant to the linked-recipient's HLA-I alleles (12.3% escape and 6.6% epitope-located). The proportion of recipient HLA target sites that were escaped in the donor was positively correlated with early set-point VL (N=145; r=0.25; p=0.003) and with the rate of CD4 decline, considering either a limit of 200 cells/ul (N=46; p=0.002) as well as of 350 cells/ul (N=46; p=0.0005). Finally, on a subset of 81 linked-recipients studied during the first two years of infection, we observed a very low reversion rate of these polymorphisms (10.9%, 6.7 and 13.6% for Gag, Pol and Nef, respectively), with polymorphisms consistent with donor escape, especially to B57/B5801, reverting more rapidly (RH=1.8; p=0.0004 and RH4.2; p=0.00002, respectively).

Conclusions: The Zambian HIV population shows a high frequency of polymorphisms in Gag, Pol and Nef proteins but only a small proportion of them may be relevant to the individual's own HLA-I alleles. This could be explained by: (1) their high probability of transmission, even when a bias for transmission of consensus residues is evidenced; and (2) their low rate of reversion, even in the absence of the selecting HLA in the newly-infected individual. This results in the transmission of pre-escaped HIV-1 variants that lead to an accelerated disease progression, with a higher set-point VL and faster CD4 decline. Nevertheless, the observation of a transmission and reversion bias for recent escapes suggests that the fitness costs of some of them will make their population-level accumulation less likely.

No conflict of interest

Abstract: 09

Virology of HIV Transmission

HIV-1 replication capacity of the transmitted virus independently predicts CD4 decline and may play a role in immune activation and memory depletion

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Introduction: Understanding how both transmitted viral characteristics and host factors influence HIV-1 pathogenesis will be paramount for rational vaccine development. Previously, viral replicative capacity (vRC), as conferred by the transmitted Gag sequence, was correlated with early set point viral load (VL) and CD4+ T-cell (CD4) decline in HIV-1 subtype C acutely infected linked recipients from Zambian heterosexual transmission pairs. However, it was unclear if early viral replication might have an impact on HIV-1 pathogenesis outside of the ability of the host immune response to control viral replication down to set point VL.

Materials and Methods: To test this, we doubled the size of the cohort under study to include a total of 127 acutely infected Zambians with longitudinal CD4 counts up to 6 years post-infection. The transmitted *gag* gene for each acutely infected individual was cloned into MJ4, a HIV-1 clade C proviral backbone, and *in vitro* vRC was assessed on a CEM-based T cell line. Kaplan-Meier survival curve analysis and Cox proportional hazard models were utilized to identify independent correlates of CD4 decline.

Results: In this larger data set, individuals infected with low vRC viruses exhibit significantly slower disease progression up to 5yr post-infection for CD4 counts <350 ($p = 0.02$), < 300 ($p = 0.002$), and <200 ($p = 0.033$). After statistical adjustment for set point VL, vRC remains an independent predictor of accelerated CD4 decline (hazard ratio = 2.05, $p = 0.005$). Individuals with the slowest CD4 decline were infected with low vRC viruses and controlled their early set point VL to less than 10^5. This effect on CD4 decline was also independent of host factors known to mediate control of set point VL, including HLA-B*57, gender, and HLA-B allele sharing between source and recipient partners.

Conclusions: In conclusion, vRC as determined by the transmitted Gag sequence significantly affects CD4 decline independent of both set point VL and host factors known influence set point VL. It is possible that HIV-1 isolates with low vRC deplete memory T cell subsets to a less severe extent and/or do not induce high levels of immune activation, which may delay disease progression. Ongoing studies evaluating the levels of inflammatory cytokines in plasma, cellular activation, and memory T cell depletion should uncover the mechanistic basis for vRC's contribution to early stage pathogenesis and further our understanding of the complex interactions between HIV-1 and the human immune system.

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Abstract: 10

Transmission of HIV Drug Resistance

The burden of transmitted drug resistance in clinical practice in Europe is increasing over time despite a stable prevalence

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Background: The SPREAD program currently monitors transmission of drug resistance (TDR) in 26 countries in Europe. In the last decade we have shown that around 10% of newly diagnosed HIV-1 patients in Europe is infected with a virus that harbours transmitted drug resistance mutations. We determined the prevalence of TDR in Europe in 2008-2010 and estimated the total number of HIV-1 diagnoses with TDR in Europe over time.

Methods: Clinical and virological data from 8479 patients diagnosed with HIV-1 in 2002-2010 were analyzed. Resistance testing was performed on samples drawn within 6 months of diagnosis. TDR (as defined by the 2009 WHO list) was determined as the weighted sum of the prevalence per risk group per country, considering their share in the European HIV-1 epidemic. To estimate the annual number of HIV-1 diagnoses with TDR for the 19 countries that participated in surveillance since 2003 (Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Poland, Serbia, Slovenia, Spain, Sweden), the weighted prevalence was multiplied by their total number of new HIV-1 diagnoses as reported by ECDC.

Results: In 2008-2010, mutations associated with resistance to NRTIs were observed most frequently (5.1%; 95% CI: 3.6 - 6.6), followed by NNRTIs (3.7%; 95% CI: 2.3 - 5.0) and PIs (2.3%; 95% CI: 1.3 - 3.2). The overall prevalence of TDR was 9.2% (95% CI: 7.3 - 11.1). Given the increasing number of HIV-1 diagnoses in these 19 countries, the estimated annual number of new diagnoses with HIV-TDR increased from 1010 (95% CI: 876 - 1144) in 2003-2005 to 1370 (95% CI: 1127 - 1613) in 2008-2010 (p0.01). For clinical practice, NNRTI-resistance mutations are of particular interest since these mutations generally confer high-level resistance to NNRTIs, a drug class frequently used as first-line therapy. The estimated number of new diagnoses with NNRTI-resistance mutations increased from 336 (95% CI: 255 - 418) in 2003-2005 to 550 (95% CI: 376 – 724) in 2008-2010 (p 0.03).

Conclusion: The prevalence of TDR in Europe remains stable around 10%. However, with increasing numbers of new HIV-1 diagnoses, the burden of TDR in clinical practices is increasing. This underlines the importance of baseline genotypic testing and continuation of surveillance of TDR.

Abstract: 11

Transmission of HIV Drug Resistance

HIV Resistance to Dolutegravir (DTG) is unlikely to be transmitted since DTG resistance mutations severely diminish both Integrase and viral fitness

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Background: No previously drug-naïve patient entered into the phase III registrational trials for DTG has yet developed resistance against this drug. To understand this, we selected for resistance against DTG in tissue culture.

Methods: Different subtypes of HIV-1 were grown in both MT-2 cells and peripheral blood mononuclear cells over protracted periods, with the concentration of DTG being incrementally increased from an initial concentration of 0.05 nM, i.e. 4 times less than the EC50. After a total of 6 months of growth, a final drug concentration of 50-100nM was achieved, beyond which virus could no longer be grown. Viral DNA was then sequenced to reveal the presence of mutations that might be responsible for resistance to DTG, and the biological relevance of these mutations was confirmed through site-directed mutagenesis experiments in which individual mutations or combinations of mutations were studied in comparison with wild-type (wt)virus in tissue culture and with recombinant HIV integrase enzyme in biochemical studies.

Results: The most common integrase resistance mutation to arise in subtype B and recombinant A/G viruses was R263K followed by E138K or H51Y. In the case of subtype C viruses, G118R frequently arose followed by either E138K or H51Y. R263K alone conferred an approximate 3-fold level of resistance to DTG in culture, a 30% drop in levels of recombinant integrase strand transfer activity, as well as an approximate 20-30% loss in viral replicative capacity. R263K together with either E138K or H51Y resulted in about 6-fold resistance to DTG as well as a far more dramatic ≈ 80% decrease in viral replication capacity and a ≈ 75% loss in integrase enzymatic activity. In addition, biochemical experiments indicated that the $t_{1/2}$ residency times of DTG for wt and R263K integrase were 26h and 16-22 hours, respectively, whereas, H51Y, by itself did not significantly affect either strand transfer activity or resistance to DTG.

Conclusions: R263K and E138K or H51Y can combine to augment levels of resistance to DTG yet result in a more severe attenuation of viral replication capacity and integrase strand transfer activity than R263K alone. These data suggest that viruses containing both mutations may be at a severe replicative disadvantage and help to explain why primary resistance to DTG has not occurred in clinical studies performed to date with previously drug-naïve patients. These findings further argue that HIV resistance against DTG is unlikely to be transmitted, given the severe fitness impairment imposed by the combination of mutations responsible for resistance to this drug.

No conflict of interest

Abstract: 12

Biomedical Approaches of HIV prevention of transmission

Optimal geographic resource allocation strategies for controlling HIV epidemics in Sub-Saharan Africa

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Background: Biomedical HIV prevention tools may soon be rolled out in Sub-Saharan Africa, but their availability is likely to be limited. Currently it is not known how to maximize the epidemic-level impact of an inadequate supply of prevention resources. We present a methodology for solving this maximization problem. Our approach is based on utilizing the significant within-country geographic variation in HIV prevalence that is found in Sub-Saharan Africa. We illustrate our approach by identifying optimal resource allocation strategies for the potential rollout of a limited supply of microbicides in South Africa. Optimal strategies maximize, under resource constraints, the number of HIV infections prevented (IP).

Material & Methods: We developed a spatially-explicit HIV transmission model and coupled it with a resource allocation model. The coupled model is used to predict the impact of geographic resource allocation strategies, and identify optimal strategies. Spatial demographics and geographic variation in HIV prevalence are modeled. Demographic, epidemiological, treatment and behavioral data from South Africa are used for parameter estimation; microbicide effectiveness is estimated from clinical trial data. Monte-Carlo filtering is used for calibration. Optimal allocation strategies are identified by analyzing model predictions using optimization techniques; specifically, a greedy algorithm.

Results: The efficiency of microbicides in reducing transmission shows significant geographic variation. It is highest in KwaZulu-Natal: 110 (median) person-years are needed to prevent one infection in women, and 320 (median) person-years to prevent one infection in men. Efficiency is lowest in the Western Cape: 450 (median) person-years are needed to prevent one infection in women, and 1,610 (median) person-years to prevent one infection in men. Variation in efficiency is due to geographic variation in HIV incidence. The higher the incidence before microbicides are introduced, the more efficient microbicides are in reducing transmission. Efficiency is a non-linear function of initial incidence. Where incidence is very high (e.g., 10%/year) microbicides would be extremely efficient in reducing transmission; only ~20 women-years would be needed to prevent one infection. There are significant geographic differences in cost-effectiveness due to the geographic variation in incidence. In terms of IP, it ranges from a high of 2.56 IP per 10,000 microbicides in Mpumalanga to a low of 0.85 IP per 10,000 microbicides in the Western Cape. If the unit cost is $0.10, cost-effectiveness ranges from $391 per IP (Mpumalanga) to $1,176 per IP (Western Cape). The optimal allocation strategy is 'all or nothing'; some regions within a country should receive no resources, whereas others should receive enough to protect all individuals. The optimal strategy prevents ~40% more infections than an allocation strategy that provides equity in access, throughout the country, to the limited supply.

Conclusions: Our results highlight the importance of obtaining a geographical understanding of generalized HIV epidemics, and demonstrate the utility of using a geographic approach for making health policy decisions. Governments in Sub-Saharan African countries will need to decide how to control their HIV epidemics with an inadequate supply of resources. Optimizing the geographic allocation of limited prevention resources could significantly increase our ability to control the HIV pandemic.

No conflict of interest

Abstract: 13

Behavioral risk factors affecting HIV Transmission

Role of medical male circumcision in HIV prevention – perceptions and their impact on sexual behaviours of adults in Kayunga district, Uganda

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Background: Medical male circumcision is now part of a comprehensive approach to HIV prevention as recommended by the World Health Organization. A major concern about the promotion of circumcision as an HIV prevention measure is the likelihood of risk compensation among those who choose to be circumcised. Men who undergo the procedure may feel less inhibited about engaging in risky sexual behaviour. This study assessed peoples? knowledge about medical male circumcision and their perceptions about the impact the procedure would have on the sexual behaviours of adults.

Methods: A cross-sectional study was carried out in Kayunga district in central Uganda. A total of 392 respondents were administered with a standardized questionnaire. In addition, 4 focus group discussions were conducted. Data was analysed using Epi Info 7.0 software. Univariate and bivariate analyses were carried out.

Results: The majority of respondents, 282 (97.5%) had heard about medical male circumcision (MMC), the main sources of information being radio 195 (34.2%) and health centres 141 (24.7%). A total of 39 (10.2%) respondents thought that MMC provided 100% protection against HIV acquisition whereas 127 (33.3%) said 1-5 weeks is sufficient time between circumcision and resumption of sexual activity. The acceptability of MMC was high as 371 (97.1%) respondents said they would circumcise their male children, 68 (80%) of uncircumcised males wished to undergo circumcision and 145 (95.4%) of females preferred to have their partner circumcised. A total of 89 (23.3%) respondents said that circumcision would compromise the use of condoms and this was associated with level of education ($p = 0.014$). The perception that circumcision increases the sexual drive of men was found to be associated with religion ($p = 0.031$) and circumcision status ($p = 0.004$). The perception that males were more likely to engage in risky sexual behaviours after circumcision was significantly associated with sex ($p < 0.001$).

Conclusion: Although several perceptions about MMC like increase in chances of engaging in risky sexual behaviours, increase in sexual drive of men and compromised condom use exist in communities which could suggest likelihood of risk compensation, they may not be significant to offset the perceived benefits of circumcision.

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No conflict of interest

Abstract: 14

Biomedical Approaches of HIV prevention of transmission

Development of advanced oligonucleotide-based microbicides: driving HIV into suicide

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Introduction: HIV is globally transmitted primarily by sexual intercourse. Therefore, a major unmet medical need is seen in the self-protection of women, particularly in societies where condoms are not accepted. Thus, user-controlled microbicides may represent promising intervention strategies that are currently being developed.

Methods: We are performing methods like RT/RNase H cleavage assay *in vitro* to show directly the specific oligodeoxynucleotide-dependent cleavage of the viral RNA sequence via viral RNase H in the highly conserved polypurin tract. Furthermore we are using luciferase-based infection assays to demonstrate reduced ability of the virus to infect cells after treatment with the oligodeoxynucleotides.

Results: We previously designed a short hairpin-looped oligodeoxynucleotide (ODN) that activates HIV-1 RNase H by mimicking ongoing reverse transcription, leading to efficient degradation of the viral RNA genome. ODNs have been shown to target cell-associated as well as free viral particles. Moreover, pronounced antiviral activity has been demonstrated *in vitro* and in several *in vivo* (animal) models. Therefore, current development focuses on strategies to increase overall ODN stability and to investigate different strategies of ODN delivery by chemical modifications of the ODNs. We could show that different chemical modifications of the ODNs did not alter the effect on RNase H dependent RNA cleavage and uptake of the ODNs into cells.

Conclusions: Taken together, these data suggest that ODNs may be valuable components of advanced antiviral microbicides that literally drive HIV into suicide.

No conflict of interest

Abstract: 15

Biomedical Approaches of HIV prevention of transmission

Increasing linkage to care for HIV-positive clients by dispensing Cotrimoxazole at the time of HIV testing and counseling

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Introduction: Annual HIV incidence in Kenya remains high at 91,000 (86,000-102,000) for adults (NACC, 2011; NASCOP, 2011). Early initiation of ART to people living with HIV (PLHIV) reduces sexual transmission in HIV discordant couples by 96% (Cohen M.S et al, 2011) and improves the individual's health outcome. HIV Testing and Counseling (HTC) is the primary entry point to prevention, care and treatment. After identification of PLHIV, effective referral is the next challenging step (Leach-Lemans, 2009). HTC providers should ensure that all PLHIV are linked and enrolled into care and treatment as only 38-45% of those in need of treatment are being reached (Kenya's National AIDS Strategic Plan III, 2009).
The Standard Ministry of Health HTC referral forms are available for completion in duplicate with the client taking the copy to the referral point, while the program staff use the other copy to track status of access to HIV Care and Treatment services. HOPE *worldwide* Kenya (HWWK) routine program data show an average of only 50% of HIV-infected clients being effectively linked. Effective referral for care and treatment for HIV-infected individuals entails access to HIV Care and Treatment services evidenced by the issuance of a clinic registration number where services are accessed. This paper looks at the effect of dispensing cotrimoxazole on linkage to care to newly diagnosed PLHIV in HTC settings. We define linkage to care as enrollment into an established care and treatment program.

Method: Counselors were trained on how to initiate cotrimoxazole preventive therapy to newly diagnosed PLHIV at the Drop in Service Centres (DISCs) where formal care and treatment services are unavailable. Clients were then asked to return for monthly cotrimoxazole at the DISCs as this increased contact between the DISCs service providers and the client, thus providing more opportunities for effective referral to an established care and treatment program. Descriptive analyses were presented as proportions and logistic regression was used to assess the differences in linkage to care between two sites; Kajiado North sub-county where cotrimoxazole was dispensed to clients and Eldoret West sub-county where cotrimoxazole was not dispensed. Results were compared for the semi-annual period October 2012 to March 2013 in the two regions.

Results: In the region where cotrimoxazole was not initiated, 225 (76% female) clients tested positive to HIV, 58% (131/225) of whom were effectively linked to care and treatment. Of those linked, 80% (105/131) were female and 66% (87/131) were aged 25-49 years. However, in the region where cotrimoxazole was initiated at HTC 75 (65% female) clients tested positive with 83% (62/75) being effectively linked. Of those linked 74% (46/62) were female and 81% (50/62) were aged 24-49 years. Our program data from the Kajiado North and Eldoret West sub-counties shows that clients who received cotrimoxazole immediately after diagnosis were significantly more likely to be linked to care ($p<0.0001$; OR =3.42, 95% C.I 1.86-6.78).

Conclusion: Initiating cotrimoxazole for newly diagnosed PLHIV in HTC settings where comprehensive services are not provided is likely to improve linkage to care and treatment

No conflict of interest

Abstract: 16

Epidemiology of HIV Transmission

Prevalence of HIV and other viral infections among Female Sex Workers in Tehran, Iran. By using Respondent-Driven Sampling

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Introduction: To find out the prevalence of HIV, HCV, HBV and HSV2 infections among Female Sex Workers (FSWs) in Tehran, A cross-sectional study by using Respondent-Driven sampling (RDS) method was conducted.

Method: From December 2011 to April 2012 Female sex workers in Tehran were included in this study by using RDS method. Inclusion criteria consisted of having experience of at least one time selling sex during the last 12 months and selling sex for at least six months in participants' lifetime. Participants were interviewed based on the structured questionnaire (demographic information ,sexual behaviors, drug history, HIV testing history, STIs symptoms and knowledge of HIV transmission,). Following it, Blood sample were collected by using Dried Blood Sampling (DBS) method for purpose of detect HIV, hepatitis C, Hepatitis B , herpes simplex virus infection and syphilis. Logistic regression analysis has been used to identify factors associated with HIV infection

Results: Among 161 Consenting participants, 5% (8) were infected with HIV. Moreover, 8.1% (13) of FSWs were HCV positive, 37.9% (61) were HSV type1, 2 positive and 1.2% (2) of participants were infected to HBV Ag. No case of syphilis was found among participants. Regarding important HIV risk behaviors, FSWs Reported using condom with their last client was 65%. While only 32.2% reported using condom in the last sex with their non-paying partners. Of participants, 25.5% have been experienced sexual abuse during last month. In addition, 55.9 % (90) have reported having symptoms of STIs during last 12 months. 25.5% (41) of participants reported using injected drug during their lifetime. Dramatically, only 20.5% had enough knowledge about HIV transmission routes. Only 32.7 %(53) of female sex workers reported being tested for HIV during last 12 months and knew the results of the test. Compared to non-infected FSWs, HIV infected FSWs were significantly more likely to test positive for HSV type1 and 2(75% vs 35.9%) , to be older(>25 years of age) , have more than six clients per week and have history of STIs in last 12 months (100% vs 59.2%).

Conclusion: Comparing with the general population of Tehran, Relatively high prevalence of HIV and other viral infections among FSWs should be considered. All in all, it is critical to commence effective counter-measures for this high risk group if the aim is to prevent spreading of these viruses to general population.

No conflict of interest

Abstract: 17

Epidemiology of HIV Transmission

Estimating the sizes of populations at risk for HIV and AIDS, Azerbaijan, 2011

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Background: Public health surveillance for HIV infection in Azerbaijan has been carried out since 1987, as serological surveillance. The findings of traditional surveillance show that prevalence of HIV infection has increased since 1987, although the number of new cases has been relatively stable during the last four years. Behavioral surveillance carried out in selected cities in 2003-2004 and 2007-2008 showed that risk of infection was greatest for injecting drug users and their sexual partners. The first study to estimate sizes of populations at risk for HIV and AIDS in Azerbaijan was carried out during August, 2010 - November, 2011.

Material & Methods: A biologic and behavioral survey (BBS) covered three groups with high risk for HIV: injecting drug users, sex workers, and men who have sex with men. Data from the BBS and from administrative data sources were used with size estimation methods recommended by UNAIDS. The multiplier method and modified method of re-capturing for small samples was determined useful for estimation.

Results: The estimated size of the population who inject drugs in Azerbaijan is 71,283±27,547, size of the sex worker population is 25,054±16,820, size of the population of men who have sex with men is 6,572±2,176. Correlation of data sources used for the estimates may make these underestimates of the true population size. Other estimates based on administrative data sources were underestimates due to limited quality of these data.

Conclusion: We conclude that the most reliable size estimates are those that are consistent with two independent methods. This first size estimation study in Azerbaijan demonstrates that estimates can be made using limited existing data, but efforts should be made to improve data quality for ongoing size estimation activities.

No conflict of interest

Abstract: 18

Mother to Child Transmission

HIV-1 Drug Resistance among Pregnant Women in Honduras

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Background: Huge efforts have been undertaken to provide access to antiretroviral therapy (ART) for prevention of mother-to-child transmission (PMTCT) of HIV-1 in resource-limited settings. In Honduras the current treatment strategy for PMTCT has change from monotherapy to combination therapy (cART). Even with the prevention role of cART, there is a possibility of the antiretroviral drugs (ARV) to induce HIV resistance and therefore its possible transmission to the child. The aim of this study was to evaluate the frequency of HIV-1 drug resistance in Honduran pregnant women, under cART between 2007-2010.

Material & Methods: Fifty HIV-1 pregnant women were recruited under the PMTCT program; 29 ARV treatment-naïve and 21 ARV treatment experienced. All women were sampled at 20-34 weeks of pregnancy (baseline) and 3-10 days after delivery (follow-up). Genotypic resistance and viral levels were tested in all of them. To determine the presence of HIV-1 resistance mutations, plasma samples were analyzed by sequencing of pol gene. For treatment-naïve women the resistance analysis was done using the Calibrated Population Resistance Tool (CPR) (version 5.0 beta, updated 01/26/10, http://cpr.stanford.edu/cpr/servlet/CPR). For treatment-experienced women the HIV susceptibility to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) were estimated with Agence Nationale de Reserches Sur le SIDA (ANRS) algorithm (July 2009, version 18).

Results: Resistance was detected in 20% (10/50) women; 10% (3/29) of them ARV treatment-naïve and 29% (6/21) in ARV treatment-experienced. In addition, one treatment-naïve woman developed resistance during prophylaxis. Twenty-two of 50 (44%) women were viremic in samples obtained within a few days following delivery despite ART prophylaxis. Mutations in all of ARV-experienced women were detected at first time point. Resistance mutations in both groups include M184V for NRTIs; K103KN, Y181C for NNRTIs; no PIs were found. Overall, resistance to NRTI drugs was observed in 20% of women, to NNRTIs in 40% and combined resistance to both drug classes in 40%. Out of the women with resistance 90% had high level of resistance to different drugs available in Honduras.

Conclusions: This constitutes the first report of prevalence of drug resistance and viremia in Honduran pregnant women. No Mother to Child transmission of HIV-1 (MTCT) were observed, nevertheless the high prevalence of resistance and viremia indicate that there was a significant risk for MTCT in this cohort, and could impact on the response of the women in their future or actual ART and limit the effectiveness of antiretroviral prophylaxis against MTCT. The present study indicates that there is a need for improvements of prevention against MTCT in Honduras, including better availability to viral load monitoring and resistance testing.

No conflict of interest

Abstract: 19

Mother to Child Transmission

Elimination of Mother to Child Transmission of HIV : Priority Countries Score Card (2013)

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Introduction: The Joint United Nations Programme on HIV/AIDS (UNAIDS) in May 2009 made a call for the virtual elimination of Mother to Child transmission of HIV . The call led to the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. The plan has two global targets of reducing new infections among children by 90% and the number of AIDS - related maternal deaths by 50% by 2015. This plan focuses mainly on the countries with highest burden of pregnant women living with HIV, otherwise known as Priority Countries.
This study accessed the progress made by the twenty of the priority countries involved in the Global Plan.

Materials and Methods: We analysed the 2009 - 2012 mid - point Spectrum estimates for 20 of the 22 Global Plan priority countries (excluding India and Uganda). The estimates were calculated using Spectrum version 4.6. The Spectrum files were developed by country teams and compiled by UNAIDS in 2013. However, the estimates from AIDS related deaths during pregnancy or within 42 days of the end of pregnancy was from 2005 to 2010.
Two overall targets and four prong targets were considered with respect to the May 2013 global targets and milestones. The data was analysed using statistical package Stata version 12.1.

Results: There was 36% reduction in the number of new infections among children from 2009 to 2012, (p= 0.0006). AIDS related deaths during pregnancy or 42 days of the end of pregnancy from 2005 to 2010 reduced by 21% (p= 0.0015), with ten of the countries achieving ≥ 25% reduction. There was a reduction in new HIV infections among women 15 - 49 years old from 2009 to 2012 by 12% (p=0.1891), however , five countries recorded increased burden of new infections.
The reduction in percentage of mother to child transmission (MTCT) ranged from 0 % to 22 % among the countries while the percentage of women receiving antiretroviral medicines to prevent MTCT reduced by 4% in Angola but increased by 72% in Zimbabwe from 2009 to 2012. In 2012, only nine countries achieved >50% coverage of women/ infants receiving antiretroviral medicines during breastfeeding to prevent MTCT with only four countries having >50% antiretroviral therapy coverage among children 0-14 years old.

Conclusion: There are varying levels of progress among the priority countries with seven of the countries namely Botswana, Ethiopia, Ghana, Malawi, Namibia, South Africa and Zambia already having >50% reduction of new HIV infections in children. Nigeria, Congo, Angola and Chad are not likely to attained the Global Plan overall goal of virtual elimination of MTCT in 2015 except extraordinary steps are taken to accelerate the pace of various intervention efforts geared towards Global Plan in these countries.
All stakeholders must come together to urgently address the issue of the countries lagging behind.

No conflict of interest

Abstract: 20

Transmission of HIV Drug Resistance

Monitoring HIV-1 drug resistance in Honduras

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Background: The widespread use of antiretroviral drugs has led to the development and transmission of viral variants with resistance mutations that can be maintained in antiretroviral-experienced and -naïve individuals. In developing countries like Honduras information about the development and transmission of resistance is insufficient. The study aim was to monitor the prevalence of drug resistance in Honduran patients.

Material & Methods: Plasma samples were collected from 39 HIV-positive patients, 27 from antiretroviral-experienced adults and 12 treatment-naïve adults planning to initiate antiretroviral therapy, from one Integral Attention Center for people living with HIV (CAI-INCP) of Tegucigalpa, during April to June 2013. HIV-1 pol sequences were generated to identify drug resistance mutations. The 2013 IAS-USA drug resistance mutation (DRM) list was used to evaluate development of resistance in antiretroviral-experience patients and the WHO list of surveillance DRM to evaluate transmitted drug resistance (TDR). Drug resistance was scored using Stanford Algorithm.

Results: The overall prevalence of drug resistance was 79% (31/39), 93% (25/27) in antiretroviral-experienced patients and 33% (4/12) in antiretroviral-naïve patients (TDR). In antiretroviral-experienced patients the prevalence of drug resistance according to drug-class was 85% for non-nucleoside reverse transcriptase inhibitors (NNRTIs), 74% for nucleoside reverse transcriptase inhibitors (NRTIs) and 22% for protease inhibitors (PIs). The prevalence of TDR for NNRTIs was 17% and the same percentage (17%) was observed for PIs. No DRM for NRTIs were identified. Single-class drug resistance mutations were observed in all samples with TDR.

Conclusions: Treatment-experienced individuals represent a large and growing group of patients with HIV-1 infection in Honduras. Although a large proportion of these patients show undetectable plasma HIV-RNA, those who are viremic often show drug resistance mutations variants. Our study shows a high proportion of treatment-experienced patients with drug resistance. Surveillance of drug resistance mutations in antiretroviral-experience HIV-positive patients may provide useful information regarding options for rescue interventions. The high prevalence of TDR reported in this study may be due to the small sample size, but is the most recent data reported. Ongoing surveillance is clearly needed to better understand the TDR phenomenon in Honduras.

No conflict of interest

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Author Index

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