[1]National Institute of Infectious Diseases, AIDS Research Center, Shinjuku-ku, Japan, [2]National Institute of Infectious Diseases, Pathogen Genomics Center, Musashimurayama, Japan, [3]Kumamoto University, Center for AIDS Research, Kumamoto, Japan

Background: CD4MCs inhibit the gp120-CD4 interaction and can also expose masked epitopes of neutralizing antibodies on the gp120 protein. In this study, we investigated the phenotypic change in the CD4MCs resistant isolates against CD4MCs, other entry inhibitors and anti-Env neutralizing monoclonal antibodies (nMAbs).
Methods: Resistant variants were induced by five CD4MCs using the primary KP-5P virus (subtype B, R5) in PM1 cells. We constructed infectious clones with CD4MC-resistant mutation following *in vitro* selection. The susceptibility of the infectious clones to the inhibitors was evaluated using TZM-bl cells. We also simulated the gp120 3D structures by MD simulation model.
Results: Resistance against CD4MCs was associated with V255M, T375N/I, or M426I substitutions. We examined susceptibilities of these mutated clones to the CD4MCs, maraviroc (MVC), an entry inhibitor IC9564, CD4bs nMAb 3D6, and CD4i nMAb 4E9C. V255M, T375I, and M426I were associated with high level of resistance to all CD4MCs tested, while there was no substantial difference between the wild type and the mutated clones in sensitivity of MVC and IC9564. The V255M and M426I clones became resistant to 4E9C, whereas the clone with T375I showed low sensitivity to both 3D6 and 4E9C. MD simulations of KP-5P gp120 in complex with NBD-556 showed that (i) V255M mutation abolished the interaction of NBD-556 and gp120, and (ii) M426I mutation disconnected a hydrogen bond between Lys130 and Glu429, thus the NBD-556 binding site shifted different from the usual.
Conclusions: These data may give important knowledge for combination of NBD and other entry inhibitors or nMAbs.

P35.04
Combinations of Entry and Reverse Transcriptase Inhibitors as Candidate Microbicides

Carolina Herrera[1], Natalia Olejniczak[1], Javier García Pérez[2], José Alcamí[2], Loïc Martin[3], Oliver Hartley[4], Charles Kelly[5], Robin Shattock[1]

[1]Imperial College, Infectious Diseases, London, United Kingdom, [2]Instituto de Salud Carlos III, Madrid, Spain, [3]Comissariat à l'Energie Atomique, Giff-sur-Yvette, France, [4]University of Geneva, Geneva, Switzerland, [5]King's College London, London, United Kingdom

Background: Multiple drug combinations as microbicides have been shown to be highly effective in preclinical studies against wild type HIV-1 isolates. This study aims to assess the activity of entry inhibitors (EIs) combinations with a nucleotide reverse transcriptase (RT) inhibitor (NRTI), against resistant HIV-1 and SIV isolates.
Methods: Antiviral efficacy of dual combinations of an NRTI, tenofovir (PMPA), and EIs, a CD4 mimetic miniprotein, M48-U1, or CCR5 inhibitors, 5P12-RANTES or maraviroc; was evaluated. The combinations were assessed in cellular (TZM-bl cells and activated PBMCs) and colorectal explant models. Preincubation of cells or tissue with the drugs individually or in combination, for one hour was followed by addition of virus. NRTI-escape mutants with point mutations K65R+/− M184V in HIV-1YU.2 and SIVmac32H RT were used. Infection was determined by measurement of luciferase expression (in TZM-bl cells) or p24/p27 viral antigen in culture supernatants.
Results: All PMPA-EI dual combinations inhibited the NRTI-resistant clones in all cellular and explant models tested. The dose-response curves of combinations including M48-U1 or 5P12-RANTES reflected the activity of the EI with no increase of potency of these drugs when combined with PMPA. The same result was observed with the gel-formulated version of M48-U1. Interestingly, an increase of activity was observed for maraviroc and PMPA when used in combination against all resistant isolates tested.
Conclusions: The positive results obtained against clade B NRTI-resistant HIV-1 isolates in this pre-clinical evaluation indicate that combinations of EIs with PMPA are good candidate microbicides able to block wild-type viruses and, importantly, NRTI-resistant isolates, which have been shown to be in increasing prevalence.

HIV Incidence and Prevalence

P36.01
Participation in Clinical Research Could Modify Background Risk for Trial Outcome Measures

Andrew M. Abaasa[1], Gershim Asiki[1], Jonathan Levin[1], Ubaldo Bahemuka[1], Eugene Ruzagira[1], Freddie M. Kibengo[1], Jerry Mulondo[1], Juliet Ndibazza[1], Matthew A. Price[2], Pat Fast[2], Anatoli Kamali[1]

[1]MRC/UVRI, Uganda Research Unit on AIDS, Entebbe, Uganda, [2]International AIDS Vaccine Initiative, New York, NY, United States

Background: Data on HIV incidence and retention are needed to inform study design of efficacy trials. However, the selection criteria and interventions during an actual clinical trial could reduce HIV incidence and thus affect the statistical power. We investigated the effect of inclusion and participation in a simulated vaccine efficacy trial (SiVET) on HIV and pregnancy incidence in a fisherfolk cohort in SW Uganda.
Methods: High-risk vounteers aged 18–49 years from fishing communities 30-40 km from the MRC/UVRI research centre were recruited in HIV open cohort. High risk was defined as history of multiple sex partners, unprotected sex, STI presence and absence from home for ≥ 2 days in the preceding 3 months. Consenting volunteers with at least 3 months of follow-up, no contraindications for hepatitis B vaccine and willing to use contraception were administered a licensed Hepatitis B vaccine at 0, 1 and 6 months to mimic a candidate vaccine. The cohort was followed quarterly for a year. HIV incidence, pregnancy and retention rates were compared.
Results: Of 853 (55% men) individuals screened from Jan 2012-Feb 2014, 575 (60% men, mean age 28) were enrolled into the open cohort, 282 (73% men) of whom enrolled into the SiVET between Jul 2012-Feb 2013. In both groups there was reduction of risky behaviours, ($p < 0.05$). A total of 13 HIV incident cases occurred in 93.0 PYO [brackets 95% CI]; incidence 13.9/100 PYO [8.1-24.1] and 10 cases in 311.6 PYO; incidence 3.2 [1.7-6.0] in the open cohort and SiVET respectively. A total of 26 pregnancies were observed in 42.7 Women Years of Observation (WYO); incidence 60.9 [41.5-89.5], and 4 pregnancies (71.4WYO); incidence 5.6 [2.1-14.8] in the open cohort and SiVET respectively.

Conclusions: Although reduction in risky sexual behaviours was observed in the open cohort and SiVET, lower HIV and pregnancy incidence rates were observed in the SiVET. The low HIV incidence could impact on sample size estimates for a prevention trial.

P36.02
Trends of Reported HIV Sexual Risk Behaviour and HIV Incidence among Fisherfolk in Uganda Receiving Clinic-based Routine HIV Counseling and Testing

Ubaldo Mushabe Bahemuka[1], Andrew Abaasa[1], Eugene Ruzagira[1], Freddie Mukasa Kibengo[1], Juliet Ndibazza[1], Gershim Asiki[1], Jerry Mulondo[1], Matthew Andrew Price[2], Patricia Fast[2], Anatoli Kamali[1]

[1]Medical Research Council/Uganda Virus Research Institute Unit on AIDS, Entebbe, Uganda, [2]International AIDS Vaccine Initiative (IAVI), New York, NY, United States

Background: HIV counseling and testing (HCT) has been shown to reduce HIV risk behaviour and is central to HIV prevention programs. We investigated risk behaviour and HIV incidence trends in a fisherfolk cohort on Lake Victoria, Uganda.
Methods: HIV negative volunteers aged 18–49 years, at high risk of HIV infection and willing to undergo HCT were enrolled. At every quarterly visit, they received HCT. Condoms and STI treatment were also provided. Risk behaviour data on alcohol consumption before sex, multiple or new sex partners, condom use and exchange of gifts for sex in the past 3 months were collected at baseline and every 6 months for 2 years. We fitted multilevel logistic regression models to investigate the trends.
Results: A total of 428 (63% men) volunteers, mean age 28 years were enrolled. There were significant reductions in reported risk behaviours over the 2-year follow-up. The proportion reporting ≥ 2 partners decreased from 80% at baseline to 45% at month 6 and to 43% at month 24 for males; for females the decrease was from 42% at baseline to 13% at month 6 and to 6% at month 24; $P < 0.01$). Similarly there were significant reductions among men ($P = 0.01$) reporting new partners but of borderline statistical significance among females ($P = 0.09$). In both sexes there were significant decreases in reported non-condom use, transactional sex and in having sex when drunk. HIV incidence (in brackets 95% CI) reduced from 8.2/100 person years (5.1-13.5), to 7.3 (5.0-10.6), 6.5 (4.6-9.1) and 6.0 (4.3-8.3) at 6, 12, 18 and 24 months respectively ($p = 0.21$).
Conclusions: In this study there was a substantial reduction in self-reported risk behaviour in the first 6 months and marginal reduction in the later period. However, a modest HIV incidence reduction was observed. This calls for an urgent need for combination prevention strategies in this population.

P36.03
Development of a Risk Scoring Tool to Predict HIV-1 Acquisition in African Women

Jennifer E. Balkus[1,2], Jingyang Zhang[1], Gonasagrie Nair[3], Thesla Palanee[4], Gita Ramjee[5], Clemensia Nakabiito[6], Marthinette Taljaard[7], Baningi Mkhize[8], Zvavahera Mike Chirenje[9], Jeanne M. Marrazzo[2], Elizabeth R. Brown[1,2], Barbra A. Richardson[1,2]

[1]Fred Hutchinson Cancer Research Center, Vaccine and Infectious Disease Division, Seattle, WA, United States, [2]University of Washington, Seattle, WA, United States, [3]CAPRISA/University of Kwa Zulu Natal, Durban, South Africa, [4]Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa, [5]South African Medical Research Council, Durban, South Africa, [6]Makerere University - Johns Hopkins University Research Collaboration, Kampala, Uganda, [7]The Aurem Institute, Klerksdorp, South Africa, [8]Chris Hani Baragwanath Hospital, Johannesburg, South Africa, [9]UZ - UCSF, Harare, Zimbabwe

Background: In many African countries, women account for more than half of all new HIV-1 infections; however, not all women are at equal risk of acquiring HIV-1. A risk prediction tool that can identify women at highest risk for HIV-1 acquisition could improve prevention research efficiency and inform HIV-1 prevention activities in policy and clinical settings.
Methods: Using baseline data from VOICE (MTN-003), a randomized, double-blinded, placebo-controlled trial conducted in South Africa, Uganda and ZImbabwe that assessed safety and effectiveness of daily oral and vaginal chemoprophylaxis for HIV-1 prevention, we used standard methods for the development of clinical prediction rules to generate a risk scoring tool to predict HIV-1 acquisition over the course of one year. The predictive ability of the score was assessed by calculating area under the curve (AUC) and the score was internally validated using 10-fold cross-validation.
Results: Among 5,029 women enrolled in VOICE, 4,834 women had complete data for factors of interest and were included in the analysis; of these, 248 acquired HIV-1 within one year after enrollment (HIV incidence = 6.05% [248/4,093 person-years]). The final risk score resulting from multivariable modeling included the following baseline factors: participant age, married/living with a partner, financial or material support from partner, partner has other partners, curable STI, HSV-2 status and alcohol use. The maximum possible score was 12; 36% of participants had a score > 6 and accounted for 66% of HIV-1 infections. The AUC for the score was 0.72 and mean AUC from 10-fold cross validation was 0.70, indicating good predictive ability.
Conclusions: A discrete set of characteristics which can be easily assessed were highly predictive of HIV-1 acquisition over one year. External validation of the risk score is required to evaluate the tool's performance when applied to different populations of women at risk for HIV-1 infection in Africa.

P36.04
Age-disparate Partnerships and Risk of HIV-1 Acquisition among South African Women Participating in the VOICE Trial

Jennifer E. Balkus[1,2], Gonasagrie Nair[3], Elizabeth Montgomery[4], Anu Mishra[2], Thesla Palanee[5], Gita Ramjee[6], Ravindre Panchia[7], Pearl Selepe[8], Barbra A. Richardson[1,2], Zvavahera Mike Chirenje[9], Jeanne M. Marrazzo[2]

[1]Fred Hutchinson Cancer Research Center, Vaccine and Infectious Disease Division, Seattle, WA, United States, [2]University of Washington, Seattle, WA, United States, [3]CAPRISA/University of Kwa Zulu Natal, Durban, South Africa, [4]RTI International, San Francisco, CA, United States, [5]Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa, [6]South African Medical Research Council, Durban, South Africa, [7]Chris Hani Baragwanath Hospital, Johannesburg, South Africa, [8]The Aurem Institute, Klerksdorp, South Africa, [9]UZ - UCSF, Harare, Zimbabwe

Background: Age-disparate relationships where the male partner is older than the female partner have been associated with