

ORAL ABSTRACT SESSION 06: DYNAMICS OF HIV INFECTION AND THE IMMUNE RESPONSE

OA06-01

Multiplicity of infection by HIV-1 in injection drug users, men who have sex with men and heterosexuals

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Background: We have recently shown that transmitted/founder virus(es) can be identified unambiguously using single genome amplification (SGA) (Keele PNAS 2008; Salazar JEM 2009) and that in heterosexual transmissions approximately 80% of patients are infected by a single virus or infected cell (Keele PNAS 2008; Haaland PLoS Pathogens 2009; Abrahams JVirol 2009). Here we explore the characteristics of virus transmission in men who have sex with men (MSM) and injection drug users (IDU).

Methods: Full-length env sequences were derived by SGA from plasma vRNA from 30 acutely infected MSM and 11 IDU from North America. Modes of infection were determined by self-report. Uncloned amplicons were sequenced, aligned, and analyzed by neighbor-joining phylogenies and the Highlighter tool.

Results: Maximum within-patient diversity ranged from 0.08-7.12%. In the MSM group, 19 of 30 (63%) acutely infected subjects had evidence of a single transmitted/founder (t/f) virus and 11 of the 30 had evidence of transmission by a minimum of 2-10 viruses. In the IDU group, 4 of the 11(36%) had evidence of a single t/f virus, while the remaining 7 demonstrated transmission by a minimum of 3-19 variants. In the subjects with multiple transmissions, the median number of t/f variants was 3 for MSM and 5 for IDU. Differences in single versus multiple virus transmissions among HSX, MSM and IDU were statistically significant ($p < 0.006$).

Conclusion: The HIV-1 transmission event is different in HSX, MSM and IDU. We see single variant transmission in approximately 80% of HSX, 60% of MSM and 40% of IDU. When multiple transmissions occur, they tend to have a higher number of variants in IDU than in MSM or HSX. These findings indicate that risk of HIV-1 acquisition correlates with numbers of transmitted viruses. This, along with the phenotypic properties of these viruses (especially Env), may be important in vaccine design and assessment.

OA06-02

Monospecific expansion of SIVmac251 during acute infection masks multiple transmitted virus variants revealed during the chronic phase

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Background: Rhesus macaque challenge models to evaluate protection are important in the search for an AIDS vaccine. Many challenge protocols use high dose SIV to ensure infection of all control animals after a single challenge. Many virus variants are predicted to infect the animals under these conditions, which is different than the majority of human infections. It is important to identify both the infecting virus swarm in the stock, and the transmitted and replicating virus, to better evaluate vaccine candidates. It is important to develop macaque models predicting human vaccination outcome.

Methods: We performed single genome amplification (SGA) to identify the full env sequence or a fragment encompassing the highly variable V1/V2 region from naïve SIVmac251-challenged animals using plasma from the acute and chronic phase, as well as from the original SIVmac251 challenge stocks.

Results: The two closely related SIVmac251 stocks sequenced by SGA showed great diversity of env sequences. Most changes were within the V1/V2 region, known to be immunodominant for SIV antibody responses. Despite the stock diversity, only a very narrow selection of similar envs were detected during the acute phase in 7 of 9 animals infected by atraumatic mucosal application. In contrast, multiple diverse env sequences were found in the chronic phase, which can be traced back to the stock.

Conclusion: Multiple species cross the mucosal barrier and infect the host during a high dose mucosal infection. Interestingly, one or very few of these variants propagate early in the acute phase, but other transmitted variants emerge to prominence later. This may be the result of viral fitness, competition, founder effects, or innate mechanisms. These findings also suggest that estimating the number of transmitted virus variants by analysis during the acute phase is inaccurate, and evaluation of both acute and chronic virus is critical to identify the transmitted variants.

OA06-03

Dynamics of CTL epitope escape and reversion in an African subtype C cohort

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Background: HIV immune escape follows a predictable mutational path in response to the HLA alleles carried by an individual. The kinetics of CTL epitope escape and reversion in subtype B HIV-1 infected individuals have recently been reported, however, the inferences drawn from them were limited by the absence of information about the transmitted sequence. To address these issues, we examined Gag, Pol and Nef sequences in both partners of 148 epidemiologically-linked transmission pairs from an African subtype C cohort.

Methods: Cohabiting HIV-1 discordant heterosexual couples from Lusaka, Zambia were followed longitudinally. Despite counseling and condom provision, 7% of uninfected partners became infected each year. At this time and at three-month follow-up intervals, blood and PBMC samples were collected from both the donor (D) and recipient (LR). The gag, pol and nef genes were amplified and sequenced from virus in plasma obtained from both partners. CTL epitopes were identified using previously published HLA-linked polymorphisms.

Results: Analyses of the viruses in the linked transmission pair recipients indicated that a surprising fraction of those transmitted had polymorphisms relevant for the HLA of the LR. Specifically, 29% of LR had viruses with escaped Gag epitopes at the time of seroconversion and these escaped epitopes were present in the D virus at the time of transmission. Thus, we find that Gag escape occurs more slowly than previously reported, with only 5-15% of Gag epitopes exhibiting de novo escape within the first year, and that a majority of HLA-linked polymorphisms at one year were transmitted from the donor.

Conclusion: The study of epidemiologically-linked transmission pairs demonstrates the high rate of transmission of escaped epitopes and that this directly impacts the calculated rates of escape, which could not be accounted for in previous studies. The potential for these non-donor driven mutations to impact viral pathogenesis is under investigation.

OA06-04

The role of early T-cell responses in subjects with acute HIV-1 infection

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Background: Previous studies have shown that T-cells play an important role in the maintenance of virus set-point in early and chronic HIV-1 infection. This study investigates the role of the first T-cell responses in selecting virus escape and controlling the early peak of viremia.

Methods: To identify the single transmitted/founder virus full-length single genome amplification (SGA) virus sequencing was performed when patients were screened before seroconversion during peak viremia. Virus evolution was monitored by further serial SGA sequencing. Ex-vivo IFN- γ enzyme-linked immunospot assays and multi-parameter flow cytometry were used with peptides matching the founder virus sequence to comprehensively map the HIV-1 specific T cell responses in subjects at serial time points over the first 12 months post-screening.

Results: T-cell assays showed that HIV-1 specific T-cell responses selected non-synonymous sequence changes at different rates across the whole of the HIV-1 proteome. The first detectable T-cell responses induced virus escape within 18-34 days of screening. However, these T-cell responses were subsequently lost or diminished after the escape variant became fixed within the virus population. The majority of the later HIV-1 specific T-cell responses induced a slower rate of escape, whilst a minority did not select for escape variants over the study period. Selected sequence changes could also be attributable to reversion, compensatory mutations, other immune responses and linkage to other selected sites. Ongoing studies are exploring the mechanisms behind the few rapid sequence changes found where no T cell response could be identified.

Conclusion: The data shows that the first HIV-1 specific T-cell responses can induce rapid virus escape at times earlier than previously described. Appearing during the decline of viral load from peak viremia these T-cell responses provide some evidence that they contribute to this fall. The role of these first HIV-1 specific T-cell responses will have an impact on vaccine design.

OA06-05

Adaptation of HIV-1 to the human immune system at the population level is driven by protective HLA-B alleles

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Background: HIV undergoes extensive within-host adaptation to HIV-specific Cytotoxic T Lymphocyte (CTL) responses. However, the full extent and importance of CTL escape mutations in driving HIV evolution at the population level remains to be established.

Methods: We included 27 individuals from the Amsterdam Cohort Studies on HIV infection and AIDS with a known seroconversion date in 1985 or 2005/06 (12 and 15 individuals, respectively), of which HIV sequences were derived within a year after seroconversion. CTL epitopes were predicted using a proteasomal cleavage/TAP transport/MHC class I combined predictor. HLA-binding epitopes from the proteins P17, P24, Nef, Protease and RT were predicted for 5 common HLA-A and 3 common HLA-B alleles, as well as for HLA-B27 and HLA-B57, the HLA-B alleles most strongly associated with slow progression to AIDS. To avoid the possibility that observed CTL escape mutations were due to within-host evolution rather than adaptation at the population level, individuals expressing the particular HLA allele under investigation were excluded from the analyses.

Results: HIV strains isolated from recent seroconvertors were found to contain significantly less 9-mers predicted to bind to the 5 HLA-B alleles under investigation compared to historical HIV strains, which was not observed for the 5 HLA-A alleles. Remarkably, the reduction in the number of CTL epitopes during the epidemic was not due to adaptation to the most common HLA-B alleles, but instead to the alleles associated with slow disease progression, HLA-B27 and B57.

Conclusion: These data show that, over the past 20 years, HIV has adapted to the human immune system by decreasing the number of potential CTL epitopes presented via HLA-B, but not HLA-A, alleles, and that such adaptations can become fixed in the population. Adaptation was not related to the population frequency of the HLA alleles, but instead seemed driven by the immune selection pressure of the HLA alleles.

OA06-06 LB

Evidence of vaccine-induced changes in breakthrough HIV-1 strains from the Step trial

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Background: Vaccinations in the Step Study, designed to assess the efficacy of a T cell-based vaccine, were interrupted in 2007 after an interim analysis showed no evidence of efficacy.

Methods: To evaluate the impact of the vaccine on founder/breakthrough viruses, i.e., the viruses obtained from the earliest available specimen around the time of diagnosis, we obtained 0.5-14 HIV-1 whole genome sequences per individual from 40 vaccine and 28 placebo recipients who acquired HIV-1 infection as of December 2007.

Results: To assess whether the vaccine elicited T cells that exerted selective pressure on founder viruses, we identified known and likely class I MHC-restricted CTL epitopes in founder sequences based on each volunteer's HLA type. We calculated protein distances between epitopes in the vaccine and those in the founder sequences. Compared to the vaccine, epitopes from vaccine recipients exhibited more mutations than epitopes from placebo recipients ($p=0.02$). Potential epitopes were then identified across all infected individuals and compared to HXB2. The epitopic distances from the combination of Gag, Pol and Nef sequences (included in vaccine) were significantly higher among vaccine vs. placebo recipients ($p=0.004$). In contrast, there was no distinction between vaccine and placebo if epitopes from Env, Rev, Tat, Vif, Vpr, Vpu (not included in vaccine) were considered together ($p=0.90$). Lastly, ~10 AA signature sites in Gag, Nef, Pol (but none in Env) were found to classify vaccine versus placebo status.

Conclusion: Our data indicate that founder viruses from vaccinees diverged further from the vaccine than viruses from placebo recipients at potentially immune reactive sites. This suggests that the vaccine may have blocked the outgrowth of specific HIV-1 variants that were the most similar to the vaccine sequence and/or elicited immune responses that may have driven specific mutations among vaccinees' viruses post-infection.

ORAL ABSTRACT SESSION 07: T CELL RESPONSES TO VACCINE

OA07-01

HIV-Specific CD8⁺ T-cells of vaccinees exhibit proliferative and cytotoxic capacities comparable to those of progressors

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Background: HIV-specific CD8⁺ T-cells of long-term nonprogressors (LTNP) exhibit extraordinary per-cell cytotoxic capacity. To adapt cytotoxicity assays for vaccine trials, we compared HIV-specific CD8⁺ T-cell cytotoxic capacity with proliferation and perforin expression using cells from LTNP, viremic progressors, antiretroviral recipients with <50 HIV RNA copies/ml plasma (R_x<50) and seronegative individuals who had or had not received the Merck Ad5 trivalent vaccine.

Methods: HIV-specific CD8⁺ T-cell cytotoxic responses to HIV_{SF162}-infected CD4⁺ T-cell targets were measured at 1 hour by flow cytometric detection of granzyme (Gr) B delivery to live targets or infected CD4 elimination (ICE). Cytotoxicity, IFN- γ production, perforin expression, and proliferation of HIV-specific CD8⁺ T-cells were examined following a 6-day stimulation with HIV_{SF162}-infected CD4⁺ T-cell targets.

Results: The HIV-specific CD8⁺ T-cell cytotoxic responses of vaccinees (medians 16.8% GrB activity, 37.2% ICE) were clearly distinguishable from those of seronegative controls (1.7% GrB activity, p<0.001; 0.3% ICE, p<0.001), but were comparable to those of progressors (16.6% GrB activity, p>0.5; 37.4% ICE, p>0.5). Among vaccinees, those with the protective alleles HLA B*27, B*57, or B*58 tended to have higher responses. Vaccinee responses were significantly less than those of LTNP (50.7% GrB activity, p<0.001; 82.5% ICE, p<0.001). GrB activity and ICE were strongly correlated with HIV-specific CD8⁺ T-cell proliferation (R=0.85, p<0.001 and R=0.87, p<0.001, respectively) and perforin expression (R=0.86, p<0.001 and R=0.9, p<0.001, respectively). When measured on a per-cell basis, cytotoxicity of most vaccinees remained at the level of progressors, even with higher effector:target ratios.

Conclusion: GrB activity and ICE correlate strongly with CD8⁺ T-cell proliferation and perforin expression in expanded cells suggesting these parameters are reasonable surrogate measurements of CD8⁺ T-cell-mediated killing requiring fewer cells. GrB activity and ICE of vaccinees were similar to those of progressors, suggesting these low responses might contribute to suboptimal control in cases of HIV infection following vaccination.

OA07-02

Adenovirus vectors induce expansion of memory CD4 T cells with a mucosal homing phenotype that are readily susceptible to HIV-1 infection

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Background: In the recently halted human immunodeficiency virus type 1 (HIV-1) vaccine STEP trial individuals that were seropositive for adenovirus serotype 5 (Ad5) showed increased rates of HIV-1 infection on vaccination with an Ad5 vaccine. We undertook a series of ex vivo strategies to address the hypothesis that immunisation of Ad5 seropositive individuals with adenoviral vectors may result in activation, expansion, and trafficking of Ad5-specific memory CD4 T cells to mucosal tissues thereby increasing the number of HIV-1 susceptible targets at the initial sites of infection.

Methods: Ad5 and Ad11 antibody titers were measured in 20 healthy volunteers. Dendritic cells (DC) were generated from these individuals, pulsed with replication defective Ad5 or Ad11 and co-cultured with autologous lymphocytes. Cytokine profiles, proliferative capacity and the migration potential of the adenovirus-stimulated memory T cells were measured. The susceptibility of re-stimulated memory Ad-specific T cells to infection with a CCR5-utilising HIV-1 was also assessed by multi-colour flow cytometric analysis and p24 ELISA assays.

Results: Stimulation of T cells from Ad5 seropositive but Ad11 seronegative individuals with Ad5, or serologically distinct Ad11 vectors induced expansion of adenovirus memory CD4 T cells expressing alpha 4 beta 7 and CCR9, indicating a mucosal-homing phenotype. CD4 T cell proliferation and IFN-gamma production in response to Ad stimulation correlated with Ad5 antibody titers. In contrast, Ad5 serostatus did not correlate with total cytokine production upon re-challenge with Ad5 or Ad11. Expanded Ad5 and Ad11 memory CD4 T cells showed an increase in CCR5 expression and higher susceptibility to infection by R5 tropic HIV-1.

Conclusion: Adenoviral-based vaccination against HIV-1 in individuals with pre-existing immunity against Ad5 may result in preferential expansion of HIV-susceptible activated CD4 T cells that home to mucosal tissues, increase the number of virus targets and lead to a higher susceptibility to HIV infection.

OA07-03

Influence of preexisting vaccinia immunity on a DNA/MVA SIV vaccine, decreased cellular immunity but enhanced control of a pathogenic SIV challenge

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Background: The influence of preexisting immunity to viral vectors is a major issue for the development of viral vectored vaccines. Here we report that for a DNA/MVA vaccine, preexisting immunity to vaccinia virus (Dryvax) decreases cellular immune responses but enhances control of an intrarectal SIV challenge.

Methods: Three groups of rhesus macaques, eight per group, were studied. The Dryvax-naive and Dryvax-immune groups received the DNA/MVA SIV vaccine (DNA at weeks 0 and 8, and rMVA at weeks 16 and 24). In addition, the Dryvax-immune group received the Dryvax vaccine 1.5 years prior to the DNA prime. The control group did not receive any vaccine. All macaques were challenged intrarectally with SIV251 at 9 months after the final MVA.

Results: Following vaccination, the frequency of SIV Gag-specific CD4 and CD8 T cells were 5-10 fold lower in the Dryvax-immune group than the Dryvax-naive group. Despite their low SIV-specific T cell responses, the Dryvax-immune macaques exhibited the best control of SIV challenge with viremia 480-fold lower at peak and 40-fold lower at set point than in the unvaccinated control animals ($p=0.01$). The enhanced control in the Dryvax-immune animals was not restricted to Mamu A*01+ animals and was strongly associated with reduced colorectal virus at 2 weeks post challenge. Factors that correlated with early colorectal viral control included the magnitude of vaccine-elicited CD4 T cells displaying the CCR5 viral co-receptor, which was dampened in the Dryvax-immune animals; the presence of anti-viral mucosal IgA, which was more frequent in the Dryvax-immune animals, and the avidity of the anti-Env Ab response. The frequency of anti-viral CD8 T cells did not correlate with early colorectal viral control.

Conclusion: These results highlight important roles for vaccine-elicited CCR5+ CD4 T cells in augmenting, and mucosal IgA and high avidity anti-Env IgG in restricting the early replication of a colorectal immunodeficiency virus challenge.

OA07-04 LB

Immunogenicity of ALVAC-HIV® (vCP1521) and AIDSVAX® B/E prime boost vaccination in RV144, the Thai phase III HIV vaccine trial

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Background: The Phase III trial of ALVAC-HIV® and AIDSVAX® B/E in Thailand began in October 2003 and concluded in June 2009. Both vaccine candidates express HIV-1 circulating recombinant form (CRF) 01_AE and subtype B antigens. This study assessed whether the Phase III vaccine lots show immunogenicity comparable to the previous Phase I/II study of the identical immunization regimen.

Methods: A list of blinded samples from persons completing all 4 injections with either placebo or vaccine and remained HIV negative at the end of the trial was provided. Peripheral blood mononuclear cells (PBMC) or plasma were tested to CRF 01_AE and subtype B vaccine antigens in the following validated assays: (1) Interferon-gamma (IFN- γ) ELISpot; (2) IFN- γ /interleukin-2 intracellular cytokine staining (ICS); (3) Binding antibody (BAb). ELISpot and ICS assays measured responses to Env (92TH023) and Gag (LAI) peptide pools prior to and 6 months following the completion of immunization. BAb was measured using reciprocal dilution EIA to A244 and MN gp120 and BH10 p24 prior to and at 2 weeks following the completion of immunization.

Results: Data will be un-blinded to treatment assignment by October 2009. Analyses of post-injection responses to Env and Gag by ELISpot revealed an overall frequency of 14%, with Env responses (11%) predominating over Gag (5%). The overall frequency of ICS responses to HIV peptides in samples studied to date was 35% and was greater for CD4 (26%) than CD8 (9%) T cells, with responses to Env again predominating; 26% versus 1% Gag for CD4 and 6% Env versus 2% Gag for CD8 T cells. The frequency of BAb responses to p24 was 37% and was identical for CRF01_AE and MN gp120 (70%).

Conclusion: Cellular and humoral immune responses to the ALVAC-HIV® + AIDSVAX® B/E regimen were predominantly to HIV Env and appear similar to those seen in the earlier Phase I/II study.