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Background: The RV144 trial showed promise towards the development of an effective HIV vaccine. Antibodies to HIV Env V1V2 loop, Env-specific IgA and HLA class II DQB1*06 allele with high Env IgA were all significantly associated with risk of infection.
Methods: We used an integrated systems biology approach to identify novel correlates of immunogenicity and/or protection. Env-specific stimulated peripheral blood mononuclear cells from RV144 participants were used to test the hypothesis that innate pro-inflammatory responses would demarcate RV144 case-control groups.
Results: A case/control gene expression analysis using 133 controls and 27 cases yielded few significantly differentially expressed genes between cases and controls. To adjust for the heterogeneity and the case/control class imbalance, we employed a stratification strategy using a tree-based classification method with IgA, V1V2 and DQB1*06 as predictor variables and the infection status as the outcome. The obtained tree model showed a balanced accuracy of 61% and identified two different risk groups. Cases in the first group had low IgA titers and did not express the DQB1*06 allele. Transcriptional profiling showed downregulation of the type II interferon induced genes (Fisher enrichment test p value = 0.04) in these cases compared to controls. Cases in the second Group had high IgA and Low V1V2 titers. Transcriptional profiling showed, interestingly, upregulation of several type I interferon genes including antiviral genes (Fisher enrichment test p value = 10^{-6}) in these cases compared to controls.
Conclusions: Herein we have identified a gene expression signature, segregating case and control donors and which, counterintuitively, shows contrasting roles for innate immune response genes in conferring vaccine induced protection. These results have important implications for the development of more effective HIV vaccine strategies.

OA04.06
Loss of Viral Control in a Subset of HIV-Infected Long-term Non-progressors Is Associated with a Decline of an Array of Antiviral Responses

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Background: Understanding molecular mechanisms of natural disease control in the absence of treatment in a minor group of HIV-infected subjects, identified as slow progressors (SP), represents a logical approach towards a potential functional cure.
Methods: In the current study we aimed to identify molecular signatures associated with viral control in our Canadian cohort of HIV-infected SP (Study # CTN 247; subjects maintaining CD4 counts over 500/microliter for over 7 years, in the absence of treatment). To this end, we have identified 5 subjects that have experienced a sudden loss of viral control (average increase of viral load: 5 to 79 fold) and a decline in the absolute CD4 counts (average loss: 211 cells/microliter). We used the Illumina technology to study genome-wide transcriptional profiles in peripheral blood mononucleated cells (PBMCs) isolated from these subjects before (Visit 1) and after (Visit 2) the loss of virological control.
Results: Our analysis identified 1,381 probe sets corresponding to 1,268 genes that were differentially expressed between V1 and V2 (nominal p-value < 5%). Among these genes, 864 were downregulated and 517 were upregulated at V2 versus V1. Of note, among the down-regulated genes, several members of both innate and adaptive anti-viral responses were identified such as APOBEC3G, IL-32, the T cell receptor CD96 (known to associated with the superior quality of CD8 T cells in HIV-infected Elite controllers), Lck, LAT, JAK1, ITK and the IL-7 receptor (IL-7R). Our validation assays are currently in progress to validate the expression of these genes at the protein level.
Conclusions: Our current study takes advantage of the power of the whole genome transcriptional analysis on privileged samples from HIV-infected SP subjects before and after the loss of virological control to identify new targets for therapeutic interventions and also to identify early biomarkers to predict disease progression.

Vaccine, Viral Latency, and Cure

OA05.01
Durable Suppression of Established Transmitted Founder Replication in Infected BLT Humanized Mice by Vectored ImmunoTherapy

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Background: Recent reports in humanized mice and monkeys have found that broadly neutralizing antibodies (bNAbs) can suppress the replication of laboratory strains of HIV and SHIV while bNAb concentration remains high. Vectored ImmunoProphylaxis (VIP) results in long-lived bNAb expression following a single intramuscular (IM) injection of a specialized viral vector, and this approach has been demonstrated as a means of durably suppressing viral load. However, previous reports of VIP-delivered bNAbs for HIV therapy required prior antiretroviral drug therapy to reduce viral load to prevent escape.
Methods: Humanized BLT mice were infected IV with the REJO.c transmitted molecular founder strain of HIV. A low dose of combination antiretroviral therapy (ART) was administered to these animals for 5 weeks, followed by a single IM injection of VIP expressing VRC07 or luciferase. Mouse plasma was analyzed by ELISA to determine antibody concentration and by qPCR to determine viral load. Cellular fractions were analyzed

by flow cytometry to quantify human CD4 cells over time. After sacrifice, plasma was subjected to a clinically validated ultra-sensitive PCR-based viral load assay.
Results: We detected viral loads of 10^5 copies/mL in infected mice prior to low-dose ART treatment, which resulted in a transient reduction and rebound to pre-therapy loads. Following VIP administration, we observed a rapid increase in the blood concentration of VRC07. Mice expressing VRC07 exhibited a sharp decline in viral load to undetectable levels and an increase in CD4 cells over four weeks and this effect was sustained for the remaining 8 weeks of the study. In contrast, mice expressing luciferase exhibited increasing viral loads with concomitant decreases in CD4 cells throughout the study.
Conclusions: Our results demonstrate that VIP expressing VRC07 is sufficient to suppress actively replicating transmitted founder virus at high viral load and support efforts to move Vectored ImmunoTherapy into clinical trials with infected patients.

OA05.02
An HIV DNA Vaccine Delivered by Electroporation and Boosted by rVSV HIV-1 Gag Is Safe and Immunogenic in Healthy HIV-uninfected Adults

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Background: Eliciting HIV-specific immune responses through vaccination remains an important goal in preventing HIV. Here we present safety, tolerability, and immunogenicity data from a phase Ia trial of a novel HIV-1 multi-antigen (MAG) DNA vaccine delivered by electroporation (EP) with DNA *IL-12* adjuvant and boosted with an rVSV HIV-1 Gag vaccine.
Methods: HVTN 087 enrolled 100 healthy adults in a multicenter, randomized, double-blinded, placebo-controlled study. Participants received 3,000 mcg HIV-MAG (*gag/pol, env, nef/tat/vif*) DNA vaccine co-administered with *IL-12* DNA at 0, 250, 1000, or 1500 mcg (N=22/group) or placebo (N=3/group) intramuscularly by EP at 0, 1 and 3 months boosted by rVSV Gag vaccine or placebo at 6 months. Participants were assessed for reactogenicity, tolerability, and adverse events. CD4+ and CD8+ T-cell responses to HIV potential T-cell epitope (PTE) peptides were measured by intracellular cytokine staining (ICS) 2 weeks after 3rd and 4th vaccinations.
Results: EP was generally well tolerated. Local and systemic reactogenicity symptoms were generally mild to moderate. After the 4th vaccination some subjects experienced moderate to severe systemic symptoms and several experienced transient lymphopenia. After DNA prime, CD4+ T-cell responses to any PTE were detected in 77% of subjects and CD8+ T-cell responses in 40%. Gag-specific CD4+ T-cell response rates after DNA prime increased significantly following rVSV Gag boost, from 15% to 86%. Gag-specific CD8+ T-cell responses also increased significantly from 6% after DNA prime to 26% after rVSV Gag boost. *IL-12* DNA 1500 mcg increased the magnitude of CD8+ T-cell responses compared to no *IL-12* DNA ($p=0.02$).
Conclusions: HIV-1 DNA vaccination given by EP with *IL-12* and boosted with HIV-rVSV is safe and immunogenic. DNA/EP prime dramatically improves T-cell responses after a single rVSV boost compared with rVSV homologous prime-boost (HVTN 090). *IL-12* DNA does not increase response rates but increases the magnitude of CD8+ T-cell responses.

OA05.03
Elicitation of Immune Responses by a DNA/MVA Vaccine in ART Treated Patients in a Treatment Interruption Trial

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Background: GV-TH-01, a Phase 1 open-label trial of GOVX-B11, a DNA/MVA prime-boost regimen, in HIV infected patients on ART was undertaken to evaluate safety and vaccine-elicited T cell responses, and to explore viral rebound during analytical treatment interruption (TI).
Methods: Patients who began ART within 18 months of seroconversion and had sustained plasma HIV-1 RNA < 50 c/mL for at least 6 months were enrolled. Patients received a total of 4 inoculations at intervals of 8 weeks. 2 of pGA2/JS7 DNA (3mg) followed by 2 of MVA/HIV62B (10^8 TCID50). At 8 weeks after the last immunization, plus an efavirenz wash-out if needed, participants entered a TI phase of 12 weeks, after which ART was reinstituted. T cell responses were scored for IFNg or IL2 by flow cytometry following stimulation with Gag, Env and Pol peptides. Responses were considered positive if ≥2-fold higher than pre-vaccination.
Results: 8 of 9 men completed all vaccinations. For the 8, median age was 37.5 yrs, baseline CD4 count was 691/μL (501-1612/μl) and all had HIV-1 RNA < 50 c/mL. Median viral load prior to ART was 5.1 log10 c/mL (2.6-7.2 log10 c/mL). No serious adverse events occurred. After the 1st or 2nd MVA/HIV62B immunization, Gag-specific CD8 T cells were boosted over pre-vaccination levels in 7 out of 8 ($P<0.05$) whereas Gag-specific CD4 T cells were boosted in 5 of 8 patients ($P=0.2$). 6 of 8 patients elicited previously undetectable CD8 responses whereas 5 of 8 elicited previously undetectable CD4 responses to Gag epitopes. Gp120 or gp41-specific antibody responses were boosted in 3 of 8 patient and 2 of 8 patients respectively. Excluding one acute seroconverter, the median reduction in HIV-1 RNA at weeks 2, 6, and 12 compared to pre-ART levels was −2.2, −1.3 and −0.8 log10 c/mL.
Conclusions: This trial demonstrates the potential for GOVX-B11 to boost both T cell and antibody responses in a therapeutic setting. A placebo-controlled trial will be required to further assess the therapeutic benefit of the vaccine.