

SPECIAL SESSION: RECENT LESSONS FROM CLINICAL TRIALS

SS01-01

AIDS vaccine clinical evaluation: where are we and where can we go?

*G Nabel¹*¹NIAID, NIH, Bethesda, MD, USA

The extraordinary diversity and immune evasion of HIV has presented unprecedented challenges for vaccine development. Despite considerable progress in preclinical evaluation of vaccine candidates, including induction of potent immune responses, identification of relevant animal models, and design of immune assays to gain an understanding of correlates of protection, progress in the field is dependent ultimately on human efficacy trials. In these efforts, success has been limited. Previous trials have been informative in identifying areas that require further research, particularly the potential protective effects of T cell vaccines and possible safety concerns. Current HIV vaccine candidates target multiple internal and external gene products with the goal of inducing both cellular and humoral immunity. Adenoviral serotype 5 (Ad5), canarypox/protein, or DNA/Ad5 vaccines have been the most widely tested, and an efficacy study of the VRC DNA/rAd5 multiclade vaccine, HVTN 505, is in progress. At the same time, new serotypes and chimeric adenoviral vectors, as well as alternative viral vectors, have been developed to mitigate the effects of pre-existing immunity against vectors. Rational vaccine design has also been applied to the development of immunogens for broadly neutralizing antibodies, the next challenge for clinical translation. Future AIDS vaccine clinical trials will be affected by evolving prevention and treatment programs that will require integration into clinical trial design.

SS01-02

Clinical outcomes from the STEP study

*S Buchbinder¹, M Robertson², and A Duerr³*¹San Francisco Department of Public Health, San Francisco, CA, USA; ²Merck & Co. Inc., North Wales, PA, USA; ³HVTN, Seattle, WA, USA

Background: The Step Study randomly assigned 3000 men and women at risk of sexually-acquired HIV to receive 3 doses of MRKAd5 gag/pol/nef vaccine or placebo. Enrollment began in December 2004; vaccinations were stopped after a pre-specified interim analysis in Ad5 seronegative participants demonstrated no protective effect on HIV acquisition or early plasma viral load. Further analysis demonstrated an increased hazard ratio (HR) for HIV acquisition among Ad5 seropositive and uncircumcised vaccinees vs. placebo recipients.

Methods: Pre-unblinding data were frozen as of Oct 17, 2007. Post-unblinding data are from Oct 18, 2007 through January 23, 2009. HR compared rates of HIV acquisition among vaccine vs. placebo recipients.

Results: Post-unblinding, there were 12 new HIV infections in women, 6 each in vaccine and placebo groups. Among men, there were 26 infections in vaccinees and 22 in placebo recipients post-unblinding, with rough equivalence in the proportion of vaccine vs. placebo recipients who were Ad5 seropositive (54% vs. 59%) and uncircumcised (50% vs. 50%). Hazard Ratios for HIV acquisition calculated using combined pre- and post-unblinding data were not significantly different between Ad5 -seropositive vs. -seronegative men (HR 1.7 vs. 1.1, p value for interaction 0.3). Hazard Ratios remained significantly greater among uncircumcised than circumcised men (HR 2.2 vs. 1.1, p value for interaction 0.045). The instantaneous HR was >1 early on, suggesting a non-significant elevation in HIV acquisition among vaccinees. The instantaneous HR began to decline approximately 12 months after enrollment, and was 1.0 or less beginning at approximately 20 months. Retention and self-reported risk appeared comparable between vaccine and placebo recipients post-unblinding. There were no overall vaccine effects on HIV disease progression.

Conclusion: Vaccine effects on HIV acquisition were seen in uncircumcised, but not circumcised, men; the initial weak association with Ad5 seropositivity is further diminished. Explanations for these associations are being explored.

SS01-03

Recent immunologic findings from the Step and related HIV vaccine clinical trials

N Frahm¹ and M McElrath¹

¹HIV Vaccine Trials Network, Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA, USA

The unexpected results from the Step trial showing the overall lack of efficacy of the Merck Ad5/HIV trivalent vaccine led to extensive, in-depth analyses of both vaccine-induced and vector-specific immunity. Major research efforts are underway in the HVTN Laboratory Program to understand why a vaccine that induced HIV-specific polyfunctional T-cell responses in 90% of vaccinated participants failed to protect against infection and may even have put trial participants in some subgroups at increased risk of acquiring HIV-1 infection. This presentation will highlight our recent findings from these analyses and will reflect on their potential relevance in the design and planning the next generation vaccine strategies.

SS01-04

Interim efficacy analysis of HVTN 503/Phambili: A phase IIB test of concept trial of the MRKAd5 HIV-1 gag/pol/nef vaccine conducted in HIV-1 uninfected adults in South Africa

G Gray¹, M Allen², G Churchyard³, L Bekker⁴, M Nchabeleng⁵, K Mlisana⁶, Z Moodie⁷, B Metch⁷, O Nicholson⁸, and J Kublin⁹

¹Perinatal HIV Research Unit, University of Witwatersrand, Johannesburg, Gauteng, South Africa; ²National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA; ³Aurum Institute for Health Research, and University of Cape Town, Cape Town, South Africa; ⁴Desmond Tutu HIV Centre, Cape Town, South Africa; ⁵Medunsa HIV Clinical Research Unit (MeCRU), Medunsa, South Africa; ⁶Centre for the AIDS Programme for Research in South Africa (CAPRISA), Durban, South Africa; ⁷Statistical Center for HIV/AIDS Research and Prevention, FHCRC, Seattle, WA, USA; ⁸Merck & Co, PA, USA; ⁹HIV Vaccine Trials Network, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Introduction: In September 2007, vaccinations were suspended but follow up continued in the Phambili study, a phase IIB evaluation of the MRKAd5 gag/pol/nef vaccine in South Africa. We present an interim efficacy analysis as of 31 December 2008.

Methods: Subjects were randomized 1:1 to vaccine (V) or placebo (P). HIV-1 infection and viral load set-point were co-primary endpoints, assessed independently on the modified intent-to-treat cohort (MITT-C) with two-tailed significance tests stratified by gender.

Results: 801 of a scheduled 3000 participants were enrolled across 5 sites. Only 7% received all 3 study injections; 66% received two; and 27% received one. In the MITT-C, 41 participants (24 V; 17 P) acquired HIV-1, 32 within one year of initial vaccination (18 V; 14 P). The HIV-1 infection rate was 5.03 per 100 person-years, 95% CI (3.22,7.49) amongst V and 3.58 (2.09,5.73) in P: HR = 1.42 (95%CI 0.76-2.64), p=0.27. Women had higher rates of HIV (HR 2.8 adjusted for age, 95%CI 1.4, 5.4), HIV acquisition also varied with age: as compared to 18-20 year olds [HR: 2.9 (95%CI 1.1, 7.5) for 21-30 year olds; 3.7 (95%CI 1.2,11.5) for 31-35 year olds]. Baseline Ad5 titre was not found to be a predictor for HIV-1 infection. The geometric mean of the viral load set-points was 19,388 copies/ml for vaccinees (N=17) and 44,083 copies/ml for placebo recipients (N=16), p=0.33.

Conclusion: Vaccination with the MRK Ad5 gag/pol/nef vaccine and baseline Ad5 titre were not associated with increased HIV-1 acquisition in Phambili, findings which differed from the STEP study. Whether this relates to limited number of persons fully vaccinated differences in the effects of vaccine by gender or small sample size is as yet unclear. Women in RSA continue to have high rates of infection despite intensive risk reduction counseling.

SS01-05

Phase III trial of HIV prime-boost vaccine combination in Thailand: result of final analysis

*S. Rerks-Ngarm*¹, *P. Pitisuttithum*², *P. Kulasol*¹, and *J. Kim*³

¹Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand; ²Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; ³U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Rockville, MD, USA

Background: After ten years of continuing efforts to identify vaccine candidates appropriate for the HIV subtypes circulating in Thailand, a community-based, efficacy trial of a prime-boost HIV vaccine combination was initiated in 2003.

Methods: This is a randomized, double-blind, placebo-controlled, community trial to determine if the prime-boost vaccine strategy 1) prevents HIV infection, 2) reduces viral load at set-point among vaccinated participants who become infected. Vaccines were developed specifically for the predominant circulating HIV subtypes in Thailand (CRF01_AE and B) using a recombinant ALVAC-HIV (vCP1521) (sanofi pasteur) prime and AIDSVAX[®]gp120 B/E (GSID) boost.

Results: 16,402 HIV negative Thai adults, aged 18-30 were enrolled through the existing Thai MOPH facilities. The volunteers received either vaccine or placebo at 0, 1, 3, and 6 months and were followed at 6 months intervals for an additional 3 years. Follow-up was concluded in June 2009, with interval retention rates exceeding 95%. To date, the vaccines have appeared to be safe. No deaths related to vaccination were recorded. Negative social events from volunteers participation were few and most resolved without sequelae. Independent DSMB reviews of interim data did not result in early stoppage of the trial for enhanced HIV acquisition rate or other safety concerns. The trial data are being prepared for statistical analysis.

Conclusion: The vaccines appear safe. The trial is scheduled for final analysis in September 2009. These results will be presented.