# Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

May 21, 2012

J Graham

The RV144 trial, a prime-boost vaccine trial consisting of a canarypox vector vaccine (ALVAC-HIV) and the glycoprotein 120 (gp120) AIDSVAX B/E vaccine, showed a vaccine efficacy of 31.2% for the prevention of HIV-1 infections over a period of 42 months. As a result, further study to determine immune correlates of infection risk was conducted in the trial samples to evaluate vaccine-evoked antibody responses, innate immune responses and cellular immune responses. Many FHCRC researchers were involved in this large clinical study, including Vaccine and Infectious Disease Division's Dr. Julie McElrath and members of the HIV Vaccine Trials Network Laboratory Program, along with Dr. Peter Gilbert and colleagues in the Statistical Center for HIV/AIDS Research and Prevention (SCHARP).

Initially, 17 assay types were selected from 32 pilot assays based on the ability to detect postvaccine responses, the uniqueness of these responses, and reproducibility. From there, the antibody and cellular assays were narrowed down to six, which were chosen to determine the roles of T-cell, IgG antibody and IgA antibody responses in the modulation of infection risk. To determine whether immune response variables predicted HIV-1 infection during the 42-month follow-up period, samples obtained two weeks after the final immunization were used from 41 vaccinees who became infected and from 205 uninfected vaccinees. The statistical analysis was designed to optimize the discovery of correlates at the expense of an acceptable risk of false positives and powered to detect only strong correlates of infection risk.

When the six variables were analyzed together in multivariate logistic-regression models, IgG avidity, neutralizing antibodies, antibody-dependent cellular toxicity, and the level of HIV-1 envelope protein (Env)-specific CD4+ T cells did not significantly predict the HIV-1 infection rate. However, two variables correlated significantly with infection risk. The binding of plasma IgA antibodies to Env correlated directly with the rate of infection (estimated odds ratio, 1.54 per standard deviation (SD) increase; P=0.02; q=0.08); and the binding of IgG antibodies to variable regions 1 and 2 (V1V2) of HIV-1 Env proteins correlated inversely with the rate of HIV-1 infection (estimated odds ratio, 0.57 per SD increase, P=0.02; q=0.08). Neither high levels of Env-specific IgA antibodies or low levels of

V1V2 antibodies were associated with higher rates of infection when compared to the placebo group, suggesting that vaccine-induced IgA antibodies were not infection-enhancing.

Taken together, high levels of V1V2 antibodies may have contributed to the RV144 vaccine protection against HIV-1 infection, and high levels of Env-specific IgA antibodies may have diminished the effects of protective antibodies. Different vaccine candidates may have different immune correlates, so continued study of both antibody and cellular responses will be necessary towards development of vaccine candidates that can improve on the results of the RV144 clinical trial.

Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, *et al*. 2012. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *New England Journal of Medicine* 366:1275-86.

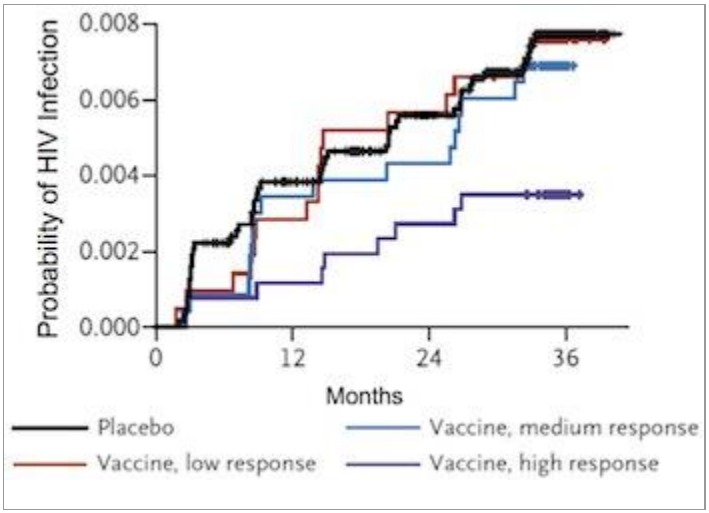


*Image courtesy of the McElrath Lab*

The estimated cumulative incidence of HIV-1 infection over time since the measurement of immune responses at week 26 is shown for the three response subgroups (IgG antibodies binding to V1V2) and for placebo recipients who were negative for HIV-1 infection at week 24.