Sequential Phase 2b Trial Design for Evaluating Multiple HIV Vaccine Regimens

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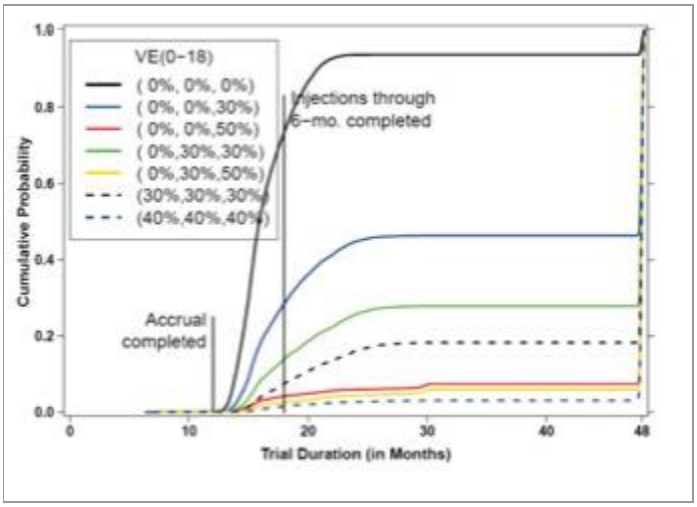
In the past 12 years, 5 preventative HIV vaccine efficacy (VE) trials have evaluated a single vaccine regimen versus placebo. One of these trials has supported partial VE of a prime-boost regimen, so there is increased interest in conducting efficacy trials that would simultaneously evaluate multiple vaccine regimens, using a shared placebo group in the same geographic region. To accelerate the pace of vaccine development, the Vaccine and Infectious Disease Division's Dr. Peter Gilbert and collaborators developed a sequential trial design for evaluating vaccine efficacy and immune correlates for multiple HIV vaccine regimens.

In the proposed trial design, VE is evaluated in two stages. The first stage covers a period of 18 months following vaccination. Then, if there is reliable evidence of vaccine efficacy, VE is evaluated in a second stage for an additional 18 months. The design is large enough to be able to select the best vaccine with high probability, based either on the first 18 months or on the full 36 months. During the first stage, measuring VE against HIV infection will allow for a fair comparison for vaccines with different temporal immunity dynamics. By simultaneously evaluating multiple vaccine regimens, the trial design allows for earlier measurements of immune correlates for the more promising vaccine regimens. Additionally, the design uses monthly HIV tests to improve the assessment of immune correlates by catching subjects in the acute, antibody-negative stage of infection, before HIV has undergone significant evolution. This allows for analysis of the originating HIV strains in a "sieve analysis", which determines how the vaccine efficacy on HIV acquisition depends on the genetics of the transmitted HIV sequence relative to the sequences represented in the vaccine.

Gilbert *et al.* applied their trial design to data from previous HIV vaccine trials, such as RV144, and they achieved results that were similar to the actual trial design, which is appropriate in this case. With the new trial design, sequential monitoring for non-efficacy, high efficacy and vaccine harm selects to weed out poor vaccine candidates, while still preventing prematurely weeding out a candidate that does not confer efficacy until most of the immunizations are received. Overall, the evaluation of this design demonstrates that testing multiple vaccine regimens through sequential

monitoring is key to providing efficient assessment of leading candidate regimens and to providing a well-powered assessment of immune correlates of protection, both of which hold promise in accelerating the pace of vaccine development.

Gilbert PB, Grove D, Gabriel E, Huang Y, Gray G, Hammer SM, Buchbinder SP, Kublin J, Corey L, Self SG. 2011. A Sequential Phase 2b trial design for evaluating vaccine efficacy and immune correlates for multiple HIV vaccine regimens. *Statistical Communications in Infectious Diseases* 3:1-86.



Distributions of the total trial duration for trials with 3 vaccine regimens versus placebo. Each line shows the cumulative probability of the trial completing over time since the trial began, for a given scenario of true values for VE(0-18).