Upgraded Statistical Machinery for Analyzing Upcoming HIV Vaccine Trials

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Over the past 14 years, five preventative HIV vaccine trials have been conducted in a randomized, double-blinded and placebo-controlled manner. One of these trials (RV144, also known as the Thai trial), which evaluated a prime-boost vaccine regimen, provided convincing evidence of modest vaccine efficacy (VE). In addition, several innovative HIV vaccine products are now becoming available for testing and may be combined into novel prime-boost combinations. Trials with these new products need improved methods for evaluating clinical endpoints if they are to be as informative as possible and bring us closer to achieving highly effective HIV vaccines.

These recent advancements have generated a great deal of motivation for a new round of phase IIb and III trials using combination prime-boost HIV vaccines (Gilbert *et al.*, 2011). The need to optimize the design of such trials and upgrade the statistical methods for evaluating their outcomes is driven by several factors, including: the huge toll that the HIV pandemic continues to take on human lives and well-being; the many challenges to designing effective HIV vaccines, which arise from both the complexities of the human immune system and the high mutability of HIV; and the large cost and lengthy duration of the requisite vaccine trials.

Ideally, immune biomarkers can be used as endpoints of successful immunization long before viral loads or survivorship measurements need to be made. Biomarkers associated with VE, such as serum titers of IgG antibodies that bind to V1V2-scaffolded Env proteins (in the case of HIV vaccines), may serve as 'principal surrogate endpoints' in vaccine trials (Gilbert and Hudgens, 2008). Good surrogates of VE can help shorten vaccine trials, reveal candidate vaccine effects of importance and guide further vaccine development efforts (Plotkin, 2010). However, because estimates of VE based on principal surrogate endpoints are conditional on an individual's potential biomarker levels, given vaccine or placebo, such estimates are generally what statistical epidemiologists call 'non-identifiable' in standard vaccine trials.

To address this limitation, Follmann (2006) developed a two-phase trial design including closeout placebo vaccination (CPV) of individuals in the trial's control arm, which is not performed in a traditional vaccine trial. Under certain assumptions, biomarkers measured after CPV theoretically can be treated as baseline covariates that should allow nonparametric estimation of disease risks in

both the vaccine and placebo groups. Yet, very little research has been done to determine the best methods under the CPV design for sampling immune biomarkers, evaluating their surrogate effects and estimating different statistical parameters describing VE conditional potential biomarker values.

These deficits were largely remedied in a paper recently published by Drs. Ying Huang and Peter Gilbert (Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center) and Dr. Julian Wolfson (Division of Biostatistics, University of Minnesota School of Public Health). The researchers' specific motivation for this study was to gear up the statistical machinery that will soon be used to analyze a phase IIb HIV vaccine trial (described in Gilbert *et al.*, 2011), which will be launched in South Africa. This forthcoming trial will utilize the two-phase CPV design for surrogate marker evaluation.

Thus, Huang *et al.* investigated the estimation of VE as a function of potential biomarker value (*i.e.*, the 'vaccine efficacy curve') in a two-arm randomization trial incorporating the innovative CPV design. They did so both analytically and via simulations, quantitatively exploring the effects of many model assumptions. Because the cost of measuring immune biomarkers is such a significant issue in large vaccine trials, the authors also investigated how different allocations of uninfected 'controls' between vaccine and placebo arms affected the efficiency of estimating different parameters of interest (see figure).

Based on their mathematical treatment, Huang *et al.* propose a brand new pseudo-score type estimator for VE that is appropriate for the augmented CPV design. Their new estimator avoids the inflated estimation error for VE that arises from incorporating closeout vaccination data into prior estimation procedures. Importantly, the authors also derive an analytic variance estimator for VE under the CPV design. This was not possible using the prior estimated-likelihood-based methods that relied solely on bootstrap resampling.

According to Dr. Huang, the research team's new approach "provides an optimal sampling design for measuring immune responses from trial participants, to provide the most powerful and efficient assessment of immune correlates of protection." Their new approach is now the state-of-the-art for HIV vaccine trial analysis. The parameter space explored by Huang *et al.* suggests that, for the upcoming phase IIb licensure trial in South Africa, a design that samples slightly more uninfected vaccinees than placebo recipients for immune biomarker measurement may be the best path to predicting the new vaccine regimen's overall effect on reducing HIV transmission.

Huang Y, Gilbert PB, Wolfson J. 2013. Design and estimation for evaluating principal surrogate markers in vaccine trials.*Biometrics*, Epub ahead of print, 14-Feb-2013, doi:10.1111/biom.12014.

Also see: Follmann D. 2006. Augmented designs to assess immune response in vaccine trials. *Biometrics* 62:1161-69.

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. *Stat. Commun. Infect. Dis.* Vol. 3, Iss. 1, Article 4, doi:10.2202/1948-4690.1037.

Gilbert PB, Hudgens MG. 2008. Evaluating candidate principal surrogate endpoints. *Biometrics* 64:1146-54.

Plotkin SA. 2010. Correlates of protection induced by vaccination. *Clin. Vaccine Immunol.* 17: 1055-65.
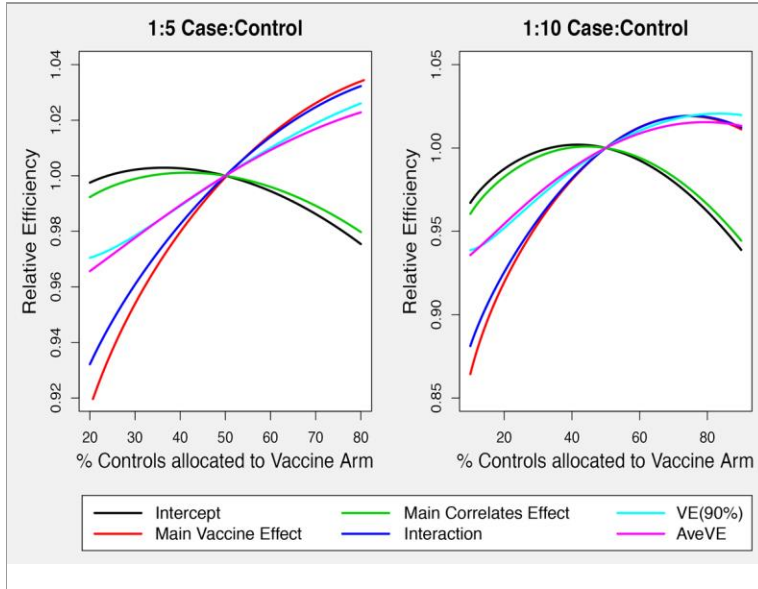
Figure provided by the authors

Variation in the asymptotic efficiencies of estimating various statistical parameters in the risk model [describing vaccine efficacy (VE) under the two-phase, closeout placebo vaccination (CPV) design] as a function of study participant allocation during the trial's second phase. A set of candidate surrogate biomarkers (S) is measured for: all infected cases in the vaccine arm; a portion of uninfected 'controls' in vaccine arm; and a portion of uninfected 'controls' in the placebo arm (i.e., the CPV component). Study cost increases (roughly linearly) with the total number of participants for which S is measured. The plot on the left represents a trial with a total cost of 5 'unit' dollars needed to measure the immune biomarkers, while the plot on the right represents a trial costing twice as much. Designs with larger allocations of controls to the placebo arm (i.e., low values along the x-axis) are better for estimating the risk model's intercept and the main correlates effect. In contrast, designs with a greater allocation of controls to the vaccine arm are more efficient at estimating the main variance effect, the interaction term, the average vaccine efficacy as a function of the potential biomarker value given assignment to the vaccine arm (AveVE) and the predicted overall efficacy of the refined vaccine as a function of the location shift in immune response for the refined vaccine versus original vaccine [VE(90%)]. See original manuscript for a complete mathematical description of the risk model and its assumptions.