Published in final edited form as:

Curr Opin HIV AIDS. 2013 September ; 8(5): . doi:10.1097/COH.0b013e328363d46a.

New Clinical Trial Designs for HIV Vaccine Evaluation

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Abstract

Purpose of review—With multiple HIV vaccine candidates suitable for efficacy evaluation in a rapidly changing HIV prevention landscape, innovative HIV vaccine trial design research is much needed to optimally utilize resources by building on lessons learned from past HIV vaccine efficacy trials.

Recent findings—Several recent articles propose new vaccine efficacy trial design strategies tailored to the emerging needs in HIV vaccine evaluation. These include a focus on efficacy evaluation proximal to the vaccination series; more intensive interim monitoring for potential harm, non-efficacy and high efficacy of the vaccine; simultaneous evaluation of multiple vaccine regimens with a shared placebo group; designs that include pilot immunogenicity studies of putative immune correlates to expedite their evaluation; as well as designs tailored to evaluate vaccine efficacy in the context of partially effective non-vaccine prevention modalities.

Summary—A more rapid evaluation of multiple vaccine candidates is possible. Weaker vaccines can be weeded out quickly. Pilot studies can be done during the trial to prepare for a timely immune correlates assessment. Evidence that emerges regarding the efficacy of non-vaccine prevention modalities will have important implications for future trial designs.

Keywords

HIV prevention; multi-arm trial; vaccine efficacy; immune correlates

Introduction

Recent proposals in HIV vaccine trial design are motivated by lessons learned from past trials and the changing scientific priorities of the HIV prevention field. The first three HIV vaccine efficacy trials, Vax003 [1], Vax 004 [2], and Step [3] found no vaccine efficacy, yet lasted 4.5, 4.5, and 2.8 years, respectively, generating interest in trial designs that could more quickly discard ineffective vaccines. The RV144 Thai trial [4], the first to demonstrate partial efficacy of an HIV vaccine, motivated a retrospective immune correlates analysis [5] that extended two years after trial completion; the long delay slowed the development of products and clinical trials motivated by its findings. This generated enthusiasm for proactively planning for immune correlates assessment within future efficacy trials [6], particularly after the successful identification of two immune correlates of risk in the RV144 trial [5]. Lastly, after several trials found positive efficacy of oral tenofovir, tenofovir vaginal gel, or oral tenofovir plus emtricitabine (TDF-FTC, Truvada®) as pre-exposure prophylaxis (PrEP) agents [7, 8, 9, 10], the ongoing HIV Vaccine Trials Network (HVTN)

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505 vaccine efficacy trial was redesigned and the designs of future vaccine efficacy trials were reconsidered in this context.

This paper reviews recent literature on HIV vaccine efficacy trial designs intended to overcome some of the limitations of past trial designs and to address the new questions and challenges raised given the changing backdrop for conducting HIV vaccine research. The topics include novel two-stage sequential Phase 2b trial designs, design features that anticipate the assessment of immune correlates, and design adaptations that accommodate the background use of non-vaccine prevention modalities (NVPs) or that provide NVPs as part of the study intervention.

The Adaptive Two-Stage Trial Design

Until the identification of an immune correlate of protection that can predict vaccine efficacy (VE), the development of an effective HIV vaccine will require multiple Phase 2b test-of-concept efficacy studies of different vaccine candidates [6]. To preserve resources and rapidly disseminate results to the field in order to advance vaccine discovery and development [6, 11], ineffective vaccines must be quickly weeded out. However care must be taken to guard against premature rejection of a vaccine for which full vaccine-induced immunity is not achieved until the vaccination series is complete, i.e., a vaccine with ramping immunity. For vaccines that show promise, durability of efficacy is of key interest. The two-phase design of Gilbert et al [6] is motivated by these considerations.

A prototype vaccine efficacy trial design enrolls HIV-negative participants who are randomized to receive vaccine or placebo, and are followed for incident HIV infection. Past efficacy trials of T cell based vaccines (e.g., Step [3], Phambili [12]) evaluated HIV acquisition and early viral load as co-primary endpoints using methods from [13]. Given the lack of efficacy for these vaccines, the field has now shifted away from T cell based vaccines which were thought more likely to reduce viral load than to impact HIV acquisition. Vaccine efficacy for preventing HIV acquisition (VE) is typically measured by one minus the relative risk (RR) of HIV infection in the vaccine vs. placebo arms. A phase 2b trial is typically powered to provide proof-of-concept evidence for vaccine efficacy and typically requires one third the number of infections of a phase 3 trial aimed at licensure [14].

Gilbert et al [15] modify the prototype design in several ways. The first novel design feature entails simultaneous evaluation of multiple vaccine regimens against a shared placebo arm. This provides resource savings and allows for head-to-head comparisons of regimens within the same trial. In addition, it boosts power for immune correlates assessment by allowing data to be pooled over multiple vaccine arms. Direct comparison of multiple regimens within the same trial need not pit one vaccine developer against another. As in RV144, regimens may consist of a prime from one developed coupled with the boost from another developer. Regimens may differ in the number of primes or boosts given or may differ in schedule.

A second feature of the Gilbert et al design is its two-stage construction. Stage 1 of the trial evaluates vaccine efficacy for each regimen over the first 18 months of follow-up. Only vaccine regimens showing positive efficacy in Stage 1 will continue to Stage 2 where durability is assessed over 0 to at least 36 months. This strategy relies on the assumption that VE is highest proximal to vaccination when the vaccine-induced immune responses are developed. The primary objective of the trial is to evaluate VE of each regimen in Stage 1. Evaluating durability of VE in Stage 2 for each regimen that shows reliable evidence of VE in Stage 1 is a secondary objective. An additional secondary objective is to compare Stage 1 efficacy among regimens to provide robust evidence about whether and which regimens to

move forward to Phase 3 testing, thereby shortening the time to a Phase 3 trial compared to separate trials of each regimen.

The two-phase design feature not only preserves resources but also shortens the time to the immune correlates analysis. When a vaccine advances to Stage 2, pilot immunogenicity studies are initiated for down-selection and optimization of immune response variables in preparation for the immune correlates analysis.

Gilbert et al recommend monitoring each vaccine regimen for potential harm, non-efficacy and high efficacy. An important component of this plan is the non-efficacy monitoring which is designed to quickly weed out weak vaccines. Non-efficacy is declared when the target level of vaccine efficacy has been ruled out with high confidence. To accommodate the potential for ramping efficacy during the immunization period, a minimum percentage of the infections must have been diagnosed after the primary immunization period in order for the first non-efficacy interim analysis to occur. Gilbert et al. demonstrate that, had such two-stage evaluation and monitoring been used in earlier HIV vaccine trials, weak vaccines would have been discarded sooner and the product development and planning of future studies, including the pilot studies for the correlates assessment of the RV144 vaccine, would have been initiated much earlier (see Table 1). The HVTN 505 trial used non-efficacy monitoring as proposed in Gilbert et al, requiring reliable evidence that the primary endpoints would not achieve the design alternative of VE=50% and a 1 log difference in set point viral load between the two groups. At the first planned interim analysis for vaccine efficacy on April 22, 2013, HVTN 505 reached its non-efficacy boundary, vaccinations were subsequently stopped and the participants unblinded. As a result of the Gilbert et al design, the trial definitively answered the primary efficacy questions at the earliest possible point.

Proactively Designing Efficacy Trials to Assess Immune Correlates of Risk and Protection

Identification of a correlate of protection is the ultimate goal in HIV vaccine development [16–24, 6, 11]. While a correlate of risk (CoR) is an immune response that is statistically associated with the rate of infection among vaccine recipients, a correlate of protection (CoP) is an immune response that is statistically associated with vaccine efficacy. A CoP may or may not be a mechanistic cause of protection [25]. Assessing a CoP is challenging because vaccine-induced immune responses are only measured among vaccine recipients; for placebo recipients, the vaccine-induced immune responses that would have been generated by vaccination are not measureable. In a seminal paper, Follman [26] proposed two statistical approaches to this problem. The first uses baseline immune predictors (BIPs), variables measured on all or a sample of study subjects at baseline that predict vaccine-induced immune responses [26, 27] to “impute” the missing vaccine-induced immune responses from placebo recipients. Another approach that may be used alone or in combination with BIPs is closeout placebo vaccination (CPV), in which the study vaccine is given to a random sample of uninfected placebo recipients at the end of the trial. Their immune responses are measured and assumed to reflect the missing immune responses that would have been measured had these subjects originally been randomized to the vaccine.

In a recent paper, Huang et al. [28] propose new methods for estimating the performance of candidate CoPs, given BIP and/or CPV designs. Analytic variance expressions were derived for some of the new estimators that facilitate answering key study design questions such as when to use CPV in addition to BIP and how many participants are needed for a well-powered analysis [28].

Future vaccine efficacy trials being planned by the HVTN will utilize some of the new immune-correlates-related design features. Importantly, these trials include assessment of potential CoRs as secondary objectives. Using methods of Huang et al. [28], the designs ensure that sufficient number of HIV infections would accrue to power assessments of identified correlates of risk as candidate correlates of protection. Both BIP and CPV design features are being considered. Assessing how vaccine efficacy varies with HIV-1 genetics as well as with host immune genetics is also of interest and being recognized as a key component of the CoP analysis.

Efficacy Trial Designs that Accommodate or Incorporate Non-Vaccine Prevention Modalities

There is growing evidence demonstrating partial efficacy of several non-vaccine HIV prevention modalities (NVPs); the most relevant for HIV vaccine trials are oral tenofovir, tenofovir vaginal gel, or oral Truvada® as PrEP [7–10]. As evidence regarding these and other NVPs emerges, the likelihood increases that some subset of vaccine efficacy trial participants will use NVPs that are not provided through the study, termed “background” NVP use. In addition, there is growing interest in trials that include both vaccine and NVPs as study interventions for the purposes of comparison and/or for studying their interactions. The combination of a vaccine and NVP may result in additive or even synergistic effects [29, 30].

Janes et al [31] propose an approach to accommodating background NVPs in a traditional two-arm vaccine vs placebo efficacy trial design. They discuss the need to increase the trial size as a consequence of NVP use, noting that power is lower under reduced placebo group incidence. Interim monitoring assesses design assumptions about NVP efficacy and its effect on incidence to ensure the trial is large enough to accrue sufficient infections for addressing primary objectives. The trial design also entails careful measurement of NVP use by trial participants, in order to achieve study objectives involving NVP use data. For example, it is of interest to estimate VE among participants using and not using NVP proximal to HIV infection, and to assess effect modification of VE by NVP use. A two-phase sampling design is proposed for measuring NVP use in a subset of trial participants according to a gold standard measurement, e.g., plasma ARV drug-level testing. HIV-infected participants and a subset of uninfected participants, sampled based on self-reported NVP use, are selected for gold standard measurement. These approaches to accommodating background NVP use were adopted in the redesign of HVTN 505 following the iPrEx study results showing partial efficacy of PrEP in a similar population [32].

As an NVP nears standard of prevention, designs that provide the NVP as part of the study intervention become more compelling. Excler et al. [29] and Janes et al. [31] consider such designs; Excler and colleagues focused on the specific case of PrEP as NVP. The scientific and statistical merits of a two-arm Vaccine + NVP vs. Vaccine-placebo vs. NVP design as well as a four arm Vaccine + NVP vs. Vaccine + NVP-placebo vs. Vaccine-placebo + NVP vs. Double-placebo design are discussed in both papers. Janes et al. [31] also consider three other design possibilities as shown in Table 2. Both sets of authors prefer the four-arm design for its ability to estimate the components of combination prevention (vaccine + NVP) efficacy; however they caution that the design may only be ethical if low-to-medium NVP efficacy is expected or the NVP is not available to the trial population.

Since many current NVPs such as PrEP pose challenges for patients with regard to sustained adherence, Excler et al. [29] suggest using a screening period to assess compliance

to the NVPM, in the context of the four-arm trial, and then enrolling only those at least 80% compliant. Janes et al. [31] instead suggest using a two-stage randomization strategy where participants are first randomized to Vaccine or Vaccine-placebo and then those willing to receive NVPM are randomized to NVPM or NVPM-placebo. The NVPM-unwilling participants can be used in the assessment of vaccine efficacy, and therefore the design can achieve its objectives with the smallest-possible sample size. This contrasts with Excler et al's [29] proposal which, by only enrolling NVPM high compliers estimates "best case" NVPM efficacy under high adherence at the expense of less generalizable study results. In addition, it allows participants who are not willing to use the NVPM to contribute data towards the evaluation of vaccine efficacy.

Conclusion

Impelled by recent results in both the vaccine and non-vaccine HIV prevention fields, HIV vaccine trial designs are growing in their flexibility, adaptiveness, and complexity. The new trial design features reviewed here provide promising strategies for conducting trials in a more resource-efficient manner while maintaining a focus on the most pertinent scientific questions in vaccine science. These approaches will play an important role in accelerating the pace of HIV vaccine development, with the ultimate goal of reducing HIV incidence at the population level.

Acknowledgments

This work was supported by UM1AI068635 from the National Institute of Allergy and Infectious Diseases, National Institutes of Health. The authors thank Peter Gilbert for his helpful comments.

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Key Points

- Promising results from the efficacy signal seen in RV144, the subsequent correlates of risk analysis, as well as lessons learned from past efficacy trials have driven new thinking about HIV vaccine trial design.
- Novel phase 2b proof-of-concept efficacy trial design features include multi-arm trials that can be used to evaluate multiple vaccine regimens against a shared placebo arm, more stringent interim monitoring to stop trials early for non-efficacious or harmful vaccines, planning for the possibility of extended follow-up to evaluate durability for regimens with significant positive early efficacy, and integration of pilot immunogenicity studies to prepare for the immune correlates assessment.
- Correlates of protection analyses have become a priority with increased effort towards identifying baseline variables to predict missing immune responses and consideration of designs that incorporate closeout placebo vaccination.
- Various trial designs have been proposed to account for background NVPM use and to include NVPMs as part of the study intervention.

Table 1

Resource savings from the more intensive monitoring of two-stage design proposal applied to past efficacy trials

Trial	Number enrolled	Trial duration (years)		Trial years spared
		Actual trial	Proposed two-stage design	
Vax 003	2,527	4.5	2.4	2.1
Vax 004	5,403	4.5	1.7	2.8
Step	1,836	2.8	2.1	0.7
RV144	16, 395	5.0	5.0	0.0

Table 2**Combination Vaccine + Non-Vaccine Prevention Modality Trial Proposals and Guidelines**

Janes et al	Excler et al	When appropriate?
Design A: <ul style="list-style-type: none"> - Vaccine + NVPM - Vaccine+ NVPM-plc - Placebo + NVPM - Plc + NVPM-plc 	2 by 2 factorial trial: <ul style="list-style-type: none"> - Vaccine + NVPM - Vaccine+ NVPM-plc - Placebo + NVPM - Plc + NVPM-plc 	Expect at most moderate efficacy of NVPM or NVPM not available to study population so that double placebo arm is warranted. NVPM-alone arm is of interest.
Design B: <ul style="list-style-type: none"> - Vaccine + NVPM - Vaccine + NVPM-plc - Plc + NVPM-plc 		Expect at most moderate efficacy of NVPM or NVPM not available to study population so that double placebo arm is warranted. NVPM-alone arm is not of interest.
Design C: <ul style="list-style-type: none"> - Vaccine + NVPM - Vaccine + NVPM-plc - Placebo + NVPM 		NVPM efficacy moderate-high and NVPM available; double-placebo arm unjustifiable. Vaccine-alone arm included to address outstanding questions about NVPM use.
Design D: <ul style="list-style-type: none"> - Vaccine + NVPM - Placebo + NVPM 	Two-arm trial: <ul style="list-style-type: none"> - Vaccine + NVPM - Plc + NVPM-plc 	Double-placebo unwarranted because NVPM is available and nearing standard of prevention, high efficacy is expected or study population is very interested in NVPM; difficult to support vaccine alone arm
Design E: <ul style="list-style-type: none"> - Vaccine + NVPM - Plc + NVPM-plc 		Double placebo warranted but not vaccine-alone or NVPM-alone since vaccine and NVPM have been co-developed and will always be provided together