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Use of Placebos in Phase 1 Preventive HIV Vaccine Clinical Trials

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Abstract

Phase 1 preventive HIV vaccine trials are often designed as randomized, double-blind studies with the inclusion of placebo recipients. Careful consideration is needed to determine when the inclusion of placebo recipients is highly advantageous and when it is optional for achieving the study objectives of assessing vaccine safety, tolerability and immunogenicity. The inclusion of placebo recipients is generally important to form a reference group that ensures fair evaluation and interpretation of subjective study endpoints, or endpoints whose levels may change due to exposures besides vaccination. In some settings, however, placebo recipients are less important because other data sources and tools are available to achieve the study objectives.

Keywords

randomization; blinding; sample sizes; clinical trial; vaccine safety; vaccine tolerability; vaccine immunogenicity

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Introduction

The development of a safe and effective preventive HIV vaccine remains the best hope to control the global HIV epidemic. Before Phase 2b or 3 efficacy trials are conducted to evaluate the effect of vaccine candidates on HIV acquisition, Phase 1 clinical trials are required to provide initial assessments of vaccine safety, tolerability, and immunogenicity in HIV-uninfected volunteers. Phase 1 testing is often carried out in sequential Phase 1a and 1b trials: once preliminary safety, tolerability and immunogenicity of a candidate vaccine regimen are demonstrated in a Phase 1a first-in-human trial, the regimen advances to further evaluation in a Phase 1b trial. Phase 1a or 1b trials are often designed as randomized, double-blind studies with the inclusion of placebo recipients (e.g. [1]). However, it is important to understand when the inclusion of placebo recipients is highly advantageous and when it is optional for achieving study objectives. In this article, we discuss considerations involving the use of placebos in Phase 1 preventive HIV vaccine trials, and suggest criteria to inform decisions about their inclusion. Several examples are based on the authors' experience in the design of Phase 1 trials within the HIV Vaccine Trials Network (HVTN).

Placebo recipients are generally important to include in Phase 1 trials

In the HIV vaccine field, where no vaccine has yet been developed with adequate efficacy to serve as an active control, placebos are used as the main control in clinical trials of vaccine candidates. These placebos are generally saline-like or vaccine diluent injections, ideally with a similar physical appearance to the tested vaccine(s), but without the HIV immunogens.

The inclusion of placebo recipients is highly advantageous in general for the following reasons, in terms of the constitution of an unbiased evaluation of vaccine candidates and provision of reference data for comparisons of vaccine candidates. For evaluating vaccine safety/tolerability, placebo recipients constitute a reference group to help ensure fair evaluation and interpretation of study endpoints in the vaccine groups. Fairness is a consequence of the randomization and blinding procedures that, respectively, ensure comparable subject characteristics between groups at the outset of the trial, and objective management and evaluation of subjective trial outcomes, such as participant-reported reactogenicity [2-6]. Although the exact extent of benefit of blinding via the inclusion of placebo participants is difficult to quantify in vaccine trials, without blinding, a participant with knowledge of having received a vaccine may be more likely to report adverse safety events than had the participant known he/she received a placebo; likewise, study staff may be more likely to attribute to the vaccine any adverse events reported by participants known to have received a vaccine. The inclusion of placebo recipients may be particularly important in Phase 1a first-in-human trials, to ensure that appropriate reference data are collected. For example, the HVTN 040/059 trials included placebo recipients in the first-in-human evaluation of an alphavirus HIV-1 clade C **gag** vaccine. Data gathered from the placebo recipients helped to demonstrate the safety of the vaccine because similar patterns of reactogenicity were observed in the vaccine and placebo groups [7]. Appropriate reference data collected from placebo recipients may be particularly valuable when a Phase

1 trial is conducted in regions of high HIV prevalence, where HIV or other infectious exposures after study entry may influence safety/tolerability.

For evaluating vaccine immunogenicity, data obtained on placebo recipients provide valuable reference information, in terms of assay specificity and assay quality, for determining whether immunological measurements on vaccine recipients represent responses due to vaccination. For example, data on placebo recipients' immune responses that are non-HIV-specific, such as cellular activation, can help inform whether the responses in vaccine recipients were altered by vaccination. In another example, when a Phase 1 trial is conducted in regions of high HIV prevalence, data on placebo recipients may also help inform whether immunological measurements on vaccine recipients were influenced by HIV or other infectious exposures that occurred after study entry. In addition, the inclusion of placebo recipients allows for the collection of validation data for the assessment of key assay qualities (e.g., false positive rates for vaccine-induced responses), which is especially useful if the trial population has not been previously studied, and when population characteristics (e.g., host genetics) could affect assay operating characteristics. Lastly, the inclusion of placebo recipients allows for the collection of in-study assay quality assurance information to enhance the interpretability of the observed data, especially those collected from relatively new assays.

Special settings when placebo recipients are not as important to include in Phase 1 trials

On the other hand, in some settings there are reasons that data from placebo recipients may be of such limited value that including placebo recipients is not warranted. First, when other data sources or tools are available, placebos may be of marginal value. Specifically, evaluations of vaccine safety/tolerability endpoints may be minimally impacted by the exclusion of placebo recipients when 1) there are sufficient historical data on the same vaccine(s) collected in similar study populations to provide evidence of safety/tolerability, or 2) there are sufficient data on similar forms of the placebos collected in similar study populations to provide background safety/tolerability data. The first type of data usually exists when closely related forms of the candidate vaccine have been studied in previous trials. For example, the VRC DNA prime-recombinant adenovirus type 5 vector boost (rAd5) vaccine has been found to be safe in more than 3,000 study participants including more than 1,500 vaccine recipients and more than 1,500 placebo recipients in the HVTN 505 efficacy trial [8] and other pre-efficacy trials [9-11]. In light of this, placebo recipients were not included in the Phase 1b HVTN 084 trial that evaluated the VRC rAd5 vaccines encoding for Gag and Pol with and without Env (Supplemental Table 1). The second type of data usually exists by pooling placebo data from clinical trials conducted during the same period of time and in similar study populations, preferably with the same administration route [12,13].

For evaluating vaccine immunogenicity, placebo recipients are less important when immune measurements are not expected to change over time for reasons other than vaccination and when baseline (prior to vaccination) specimens are available to serve as a reference for the evaluation of post-vaccination responses. The cost of storing and assaying baseline specimens is generally afforded by the savings from excluding placebo recipients. In

addition, including placebo recipients for blinding purposes may not be necessary when blinded sample labeling systems are used to ensure an unbiased immunogenicity assessment and control samples are contemporaneously tested to provide assurance of assay specificity; in our experience these are generally common in laboratories.

Another reason for considering foregoing placebos in Phase 1 trials is the limited utility of including only a small number of placebo recipients. Specifically, the sample size of Phase 1 trials is generally limited to the minimum needed to assess preliminary vaccine safety and immunogenicity, typically 2-6 placebo recipients per arm and 10-30 vaccine recipients per arm in Phase 1a-1b trials [1]. With these sample sizes, the distribution of baseline participant characteristics may be unbalanced between treatment groups due to random chance, compromising an unbiased assessment of the study endpoints. In addition, for safety/tolerability assessments, even in the unlikely scenario in which a safety event is expected to occur at a true rate of 5%, there is still a 90% or 74% chance that no such event would be observed among 2 or 6 placebos, respectively. Meanwhile, there is a 40% or 79% chance that at least one such event would be observed among 10 or 30 vaccine recipients, respectively. The magnitude of the observed treatment group differences necessary to achieve statistical significance—for example, 15/30 vs. 0/6 to achieve a 2-sided p-value < 0.05 with a Fisher's exact test—further emphasizes the limited value of including a small number of placebos to assess safety. Similarly, for immunogenicity assessments, the number of placebo recipients is generally not sufficient to provide a precise estimate of the false positive rate of an immunogenicity measurement. Furthermore, since the level of vaccine-induced immune responses is expected to be null among placebo recipients, such data may be unnecessary for interpreting responses among vaccine recipients.

A final reason for considering foregoing placebos in Phase 1 trials is that vaccine candidates are often advanced for further evaluation based on their immunogenicity compared to other vaccine candidates, rather than compared to placebo. Such comparisons are generally conducted based on immune responses measured by well-characterized laboratory assays that allow for meaningful cross-study analyses. Placebo recipients do not contribute necessary information for such assessments. Therefore, not including placebo recipients could spare resources to allow enrolling more vaccine recipients, thus resulting in more precise characterizations and comparisons of vaccine immunogenicity.

Remarks

In Table 1, we summarize design features of Phase 1 HIV vaccine trials with and without placebo recipients. In Table 2, we provide concrete scenarios to help inform decisions regarding the inclusion of placebo recipients. In general, including placebo recipients is recommended in Phase 1 studies of candidate HIV vaccines, especially in first-in-human trials, when such inclusion is highly advantageous to obtain a fair assessment of subjectively measured safety/tolerability endpoints, when there are insufficient safety/tolerability data in a similar study population, or when study endpoints may be influenced by exposures other than vaccination after study entry. Conversely, placebo recipients might be reduced in number or not included at all when sufficient vaccine and/or placebo safety data are available and when baseline specimens are feasible and appropriate to allow for an objective

evaluation of the safety/tolerability and immunogenicity of the vaccine candidate(s). These considerations may also apply to the design of early phase trials of other vaccines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. Study objectives and the research context drive the design of Phase 1 preventive HIV vaccine trials.
2. The inclusion of placebo recipients enables blinding and fair assessment of study endpoints.
3. The inclusion of placebo recipients provides valuable in-study reference data.
4. Placebo recipients are less important for vaccines with extensive safety data.
5. Placebo recipients are less important when baseline data are proper as reference information.

Table 1

Trial design features of Phase 1 preventive HIV vaccine clinical trials with and without the inclusion of placebo recipients.

Endpoint	Design Feature	Trial Design	
		Both vaccine and placebo recipients included	**Only vaccine recipients included**
Safety	**In-study control group for blinding**	Yes	No (but may blind across multiple vaccine groups)
	In study reference group for comparison	Yes (but of limited power)	No (but may use data from other studies in similar populations, with similar vaccine schedules and administration routes)
Immunogenicity	**In-study control group for blinding**	Yes	No (but may use a labeling system to blind with other samples)
	In study reference group for comparison	Yes (but of limited power)	No (but may use within-subject baseline data when available and appropriate)
Cost	**Within-study cost-saving**	No	Yes
	Overall development cost-saving	Variable, depending on the safety/tolerability and immunogenicity of the vaccine candidate	

Table 2

Scenarios encountered in the design of Phase 1 preventive HIV vaccine clinical trials, and corresponding decisions regarding the inclusion of placebo recipients.

Decision	Scenarios
Placebo recipients are highly advantageous to include	• If a fair assessment of subjective safety/tolerability endpoints is required, and there are insufficient data on safety/tolerability of the same vaccine candidate in a similar study population. OR • If measurements of study endpoints may be influenced by infectious exposures after study entry.
Placebo recipients may not be included	• If there are sufficient data on safety/tolerability of the same vaccine candidate in a similar study population, AND • If baseline specimens are feasible and appropriate to serve as controls for immunogenicity assessments.
Placebo recipients are helpful, but not essential to include	• If some study endpoints are measured by assays or tools that will benefit from further validation based on more placebo recipient samples, OR • If the characterization of non-vaccine-induced immunological measurements in placebo recipients will aid the interpretation of those measurements in vaccine recipients.