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Statistical Approaches to Accelerate the Development of Long-Acting Antiretrovirals for HIV Pre-Exposure Prophylaxis

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Abstract

Purpose of Review: This review considers statistical issues in the design and analysis of the studies used to develop long-acting formulations of antiretrovirals (ARVs) for preexposure prophylaxis (PrEP).

Recent Finding: An abundant pipeline of products is maturing. Accelerating their evaluation as clinical products requires abandonment of non-inferiority standards. Randomized trials should be based on the comparison of principled but innovative estimates of background HIV risk and enrich enrollment for those who do not desire current PrEP products. At every stage of testing, innovative analyses can be applied to help inform and accelerate later studies.

Summary: The development of new long-acting PrEP regimens can be accelerated by innovations in design, ingenuity in synthesizing data sources, and application of causal inference methods.

Keywords

non-inferiority; pre-exposure prophylaxis; HIV prevention; long-acting injectable; implant

Introduction

While the current technologies to control the HIV epidemic are promising, the prevention movement is falling far short of its goal. In 2018, the global number of HIV treatment initiations surpassed the number of new HIV infections for the first time [1]. However, the global scale-up of HIV pre-exposure prophylaxis (PrEP) with co-formulated tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) has been slow and uneven [2]. Progress in global prevention will require not only maximizing the potential of available technologies [3–7], but also the development of a richer set of options.

It is useful to consider the concept of the prevention mosaic, which shows that the population in need of HIV prevention technologies may be served by some technologies but not others. Alternative delivery methods (e.g., an implant, microbicide, or injectable) appear to be acceptable to many individuals who are not interested in oral PrEP [8,9]. It is hoped

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these options will cover more tiles in the prevention mosaic. A formidable pipeline is looming [10]. This paper addresses the statistical and design issues regarding the clinical development of long-acting ARV-based PrEP products (LA-PrEP).

Formative Data for Phase III Trials

Animal studies have been used in the proof of concept for the effectiveness of potential PrEP agents. They provided key data regarding oral TDF/FTC as a PrEP [11] as well as important information about the protective levels of the first drug formulated into LA-PrEP [12,13]. This was particularly important since these studies are based on single doses or short treatment courses with potential anti-PrEP agents. Administration of a dose of long-acting injectable cabotegravir (CAB-LA) provided evidence that CAB-LA might be used as a PrEP and suggested required concentrations for protection. Statistically, these results might support estimation of not only a single target but also a gradient of protection, which might serve as a prior distribution in a Bayesian analysis of the drug concentration and its protection of humans.

Phase II trials have been proven to be critical for the selection of the dose and administration schedule for CAB-LA [14,15] and are likely similarly important for other long-acting products. These phase II data provide information about pharmacology, tolerability, and acceptability. A concentration relationship could be used to compare extrapolated levels of protection to indicate the magnitude of differences between doses. A similar approach was used to estimate the protection provided by different dosing intervals for oral TDF/FTC [16].

Phase III Efficacy Trials

Clinical development of an HIV PrEP agent requires a foundation of randomized trials with HIV incidence as an outcome. Efficacy trials must ethically contend with the fact that oral TDF/FTC is an effective HIV PrEP regimen, which is broadly recommended, and must make provisions to promote its use, link service, or provide PrEP to study participants. This has major implications for trial design. Two major options include active controlled or enrollment of those who initially decline oral tenofovir-based PrEP.

Recently, launched trials for PrEP agents have been double-blind double-dummy active controlled trials (see Table 1). These trials require a large number of participants and a large total follow-up. Drivers of the sample size include the degree of difference to be ruled out (under the null hypothesis), expected degree of advantage of the novel method (under the alternative hypothesis), and seroconversion rate in the trial.

These power demands are more daunting than they appear. Donnell [17**] considers power issues and demonstrates that the sample size for a non-inferiority trial based on a study with high adherence to a product would result in prohibitive sample sizes. Studies of this size are infeasible because they would exhaust the precious resources of time, participants, and resource dollars at the same time that the prevention pipeline is increasing. For this reason, it appears that non-inferiority is not a workable framework for demonstrating that LA-PrEP agents are effective, and alternatives are urgently needed [17**, 18**, 19*].

Alternative Lines of Evidence — Active Controlled Trials

The most difficult scenario is a randomized trial of standard of care (SOC) versus LA-PrEP, where both arms are substantially protected against HIV infection, yielding a very low seroconversion rate. A low seroconversion rate in a population selected for high risk sexual practices tends to suggest efficacy. However, a low seroconversion rate could be due, at least partially, to lack of contact with viremic partners (e.g., partners on PrEP or TASP). Strong evidence if seroconversion rates in both are were sharply lower than in a concurrent randomized arm that received no PrEP. A no-PrEP arm provides a direct way to estimate effectiveness and the number of infections averted by SOC and by LA-PrEP. These could be compared using the averted infection ratio (AIR) [20**], an index of their comparative effectiveness. For instance, showing that the lower bound of the 95% confidence interval for the AIR is greater than approximately 0.50 could be substantial evidence that an LAI PrEP agent preserves a substantial proportion of the SOC effectiveness.

However, a randomized concurrent no PrEP arm raises practical and ethical issues [21**]. A variety of approaches have been proposed to reconstruct one based on trial data. One approach is to muster various lines of evidence about trial participants to reconstruct a counterfactual “no PrEP” arm yielding a direct estimate of the background HIV incidence.

Alternative Lines of Evidence — Estimating Background Incidence

Sexually Transmitted Infections

One approach leverages evidence of ongoing condomless intercourse through using data on incident on-trial sexually transmitted infections (STIs). Mullick and Murray [18**] showed that in cohorts of men who have sex with men and transgender women (MSM/TW) without PrEP use, the background HIV incidence is tightly correlated with the rate of diagnosis of rectal gonorrhea, and they formally derived the relationship. Both STIs share the common risk practice of receptive anal intercourse. Hence, a high rectal gonorrhea rate provides an objective measure of ongoing sexual practices and suggests HIV susceptibility but does not guarantee that partners are viremic.

Pre-Enrollment and Recent HIV Infections

Another approach examines evidence of HIV risk just prior to study entry. One could examine participants who were screened for the trial and were excluded because they were HIV+. Assuming stable HIV incidence in the screening cohort, then laboratory evidence of recent infection [22] can provide an approximation of the background HIV incidence. This approach is promising, particularly in settings without frequent HIV testing. A similar method estimates HIV incidence from the proportion of participants who are acutely infected at the trial’s randomization visit, evident as being HIV screening test-negative but with viremia. This provides a clear numerator, and the denominator is provided by the window period of the screening assay. A major disadvantage of this approach is that with the introduction of fourth-generation HIV screening tests, the window period is now very short. It would take a trial with both a high background risk and the enrollment of a large number of participants to give a reasonably precise estimate of the pre-enrollment background

incidence among the population. Further, the pre-enrollment background rate may not reflect the background incidence for the duration of the trial.

HIV Risk Scores

HIV prevention cohorts that enroll a well-characterized HIV-negative population and follow them at regular intervals for HIV infection are an invaluable resource. A cohort from a context without PrEP (e.g., a pre-PrEP cohort or a placebo arm from a PrEP trial), is ideal for forming predictions for incident HIV infection based on baseline demographics and HIV risk practices. Risk scores have been developed for populations of young African women [23], discordant couples in Africa [24], and for MSM in the United States [25]. An active controlled trial could enroll participants and collect the baseline factors that comprise the risk score, providing a ready estimate of the expected background HIV risk in the cohort (in the absence of PrEP).

In other cases, era, geography, or other context may cast doubt on whether such a model produces valid estimates. This could happen if the context was not represented in the model building (e.g., MSM in Latin America), if interviewer rapport is important for accurate reporting of sexual practices, or if PrEP and TASP have become more common in the trial population than the model-building population.

Comparison to Population HIV Incidence Rates

Another approach attempts to reconstruct contemporaneous local controls by relying on surveillance data. In these cases, local HIV surveillance data would be used to infer the background HIV incidence rate among the local population not currently on PrEP. This has the advantage of accounting for the regional difference in epidemics, and in particular, uptake of TaSP and PrEP. Such a counterfactual analysis was applied to the DISCOVER study [26**], although the analysis was limited to study sites in the USA.

The trial population background incidence may differ from the surveillance rate because the trial population may differ in important demographic factors, sexual practices, and HIV testing frequency. Yet, it seamlessly handles issues reflecting the time period and region from which study subjects are drawn. A major limitation of this approach is that it can only work in locations with rigorous estimates of the size of the at-risk population and new HIV diagnoses.

Back Calculation Based on Adherence

Another approach might be attempting to leverage adherence data with trial incidence rates. For instance, using drug level it is possible to get a sense of the aggregate adherence in the TDF/FTC arm. Using data that links drug levels to reduction in HIV [27*,28] would permit estimation of the aggregate HIV risk reduction due to adherence to TDF/FTC on a daily oral TDF/FTC arm. The observed incidence on the TDF/FTC arm could be upweighted by the degree of protection to produce a plausible estimate of the background incidence. This approach is reliant on bridging from previous studies linking adherence to protection. While completely internal, upweight must contend with the possibility of confounding between factors that affect both adherence and HIV risk practices. For instance, if high-risk

participants have low adherence, then the observed adherence rate among the non-adherers is higher than the background rate for the cohort.

Focus on Ùnmet Need”

Reflecting the prevention mosaic, it may be worthwhile to focus trials of LA-PrEP agents in who do not find existing prevention options appealing or acceptable. A trial could enroll participants who decline oral TDF/FTC or other proven PrEP agents. It might be blinded, include a comprehensive prevention package, and randomized to LA-PrEP or a matching placebo [17**]. For instance, a vaccine trial, HVTN 706 [29], plans to enroll participants who do not want to receive oral PrEP. Such a trial carries a high burden ethically to ensure that the participant’s risk of HIV is minimized [21**].

This design provides a straightforward estimate of the effectiveness of LA-PrEP alone from the intent to treat (ITT) comparison of the randomized arms. However, adoption of oral PrEP during the trial could complicate interpretation. Second, the interpretation of the ITT effect is that of the effectiveness of the initial choice of using LA-PrEP for prevention in a low-propensity population and a context in which tenofovir-based PrEP is available. It may not reflect effectiveness in other populations.

Donnell [17**] also considered a hybrid design. Those open to the SOC would be enrolled in an active controlled trial. Those who decline the SOC would be enrolled in a placebo-controlled trial. This hybrid trial is very provocative, and the placebo control provides direct evidence of effectiveness in the “unmet need” stratum. However, it may also be leveraged to provide an estimate of the background incidence for the active controlled trial. Further, investigation of the power and analytic possibilities of the “unmet need” trial alone or combined with an active controlled trial would greatly assist in the planning of LA-PrEP trials.

Estimating Efficacy

ITT analysis estimate of the population level effects of offering the LA-PrEP agent by counting HIV infections resulting from ineffective PrEP use as failures of the product. However, it is compelling to estimate how well the product prevents HIV infections when used as directed by the trial. We refer to this as the product’s “efficacy.

Calculating efficacy quantities is as challenging as it is compelling. It requires linking HIV risk to LA-PrEP adherence data. A major advantage of LA-PrEP adherence data is adherence to the LA-PrEP (implant, injections) is directly observed. Complications will involve participants who miss visits, fall off the LA-PrEP administration schedule, and test positive at their next visit. HIV infection could have occurred before or after the participant’s missed visit/injection. Methods for “dating” the HIV infection and testing of LA-PrEP drug levels would be important for determining whether the HIV infection occurred before or after the participant became non-adherent.

Estimation of efficacy is conducted among adherent participants and is a major obstacle in the confounding between HIV risk practices and LA-PrEP adherence. It is plausible that

these confounders can vary with time (e.g., condomless anal intercourse or a new partner). This is known as time-dependent confounding and requires specialized methods to address, such as marginal structural models with inverse probability weighting [30].

Rigor in addressing questions of efficacy will then require ensuring regular follow-up even among participants who no longer desire injections, using laboratory techniques that can date infections, collecting a rich set of potential time-dependent confounders of adherence, and use of advanced statistical techniques like marginal structural models.

Bridging to Special Populations or Alternative Delivery

The relationship between drug level and efficacy would permit estimation of the EC_{90} or EC_{95}. This could use a Bayesian framework, with the prior distribution for the concentration to efficacy relationship developed from animal challenge experiments.

The EC_{90} provides critical information for future studies. Pivotal trials may under-represent some special populations (e.g., trans individuals, adolescents). Demonstrating that the use of LA-PrEP in this population, possibly after directly observed administration, leads to protective levels (near or at the EC_{90} or EC_{95}), may provide strong proof of concept for efficacy. In addition, clinical guidance will require estimates of the timing of onset of protection as well as the loss of protection. EC_{90} estimates combined with focused pharmacokinetic studies can help provide information about the starting and stopping of a drug [16,31] as well as guidance about the clinical significance of any pharmacologic trial after discontinuation.

It could also be used to support bridging to alternate administration. For instance, if a clinical trial leads to positive results for an EC_{90} or EC_{95}, it might support bridging with results from formulas with the same active agent, such as an implant.

Conclusion

Realizing the potential of ARV-based PrEP requires that we scale up existing tools and streamline the development of new ones. This will require attention to rigorous trials that leverage estimates of background HIV incidence and can enroll those with unmet prevention needs. It is also important to maximize the yield from these trials by estimating efficacy and protective concentrations. Every effort should be made to exploit pooling of data across studies, collecting key data early in the pipeline, and using innovative designs and statistical methods. Our task is time-critical, and we must rise to this unprecedented challenge.

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Table 1:

Trial Sizes and Power Calculation for Active Controlled Trials with TDF/FTC Control Groups

Trial	Incidence Rate Ratio		Required		
	Null Hypothesis	Alternative Hypothesis	Incident HIV+	Participants	Person Years
DISCOVER *,1	1.62	1.00	106	5,400	8,756
HTPN 083 +,1	1.23	0.75	174	4,500	10,400
HPTN 084 +2	1.00	0.54	111	3,200	7,200

+ randomization: Injectable cabotegravir v. Daily oral tenofovir disproxil fumerate/emtricitabine

* randomization: Daily oral tenofovir alafenamide/emtricitabine v. Daily oral tenofovir/emtricitabine

1. Population: men who have sex with men and transgender women

2. Population: cis women in subsaharan Africa