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Ethical Considerations regarding Oral PrEP in HIV Prevention Trials

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Abstract

Purpose of review—Although substantial evidence supports oral pre-exposure prophylaxis with tenofovir disoproxil fumarate and emtricitabine (OPTF) for the primary prevention of HIV infection in certain settings, assessing whether other promising HIV prevention interventions are safe and effective as well as determining optimal prevention strategies necessitates research. However, given the established safety and efficacy of OPTF, it is necessary to determine when and how is it ethically acceptable to conduct this research, which is the focus of this review.

Recent findings—Although they are somewhat intertwined, questions regarding OPTF in research can be considered in two broad categories: use in a comparison arm and as a standard of prevention. Major statements addressing these issues are described and recent literature directed at the particular issue of OPTF in research is reviewed and critiqued.

Summary—There is now arguably a rebuttable presumption for the use of OPTF as a comparator or as part of the standard of prevention in much future HIV prevention research. However, making such determinations necessitates taking into account scientific considerations, the modality being evaluated, acceptability, adherence and the local context. Doing so should be optimized by robust stakeholder engagement.

Keywords

preexposure prophylaxis; HIV infection; ethics; research ethics; comparator arm; standard of prevention

Introduction

Substantial evidence supports daily oral pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate and emtricitabine (OPTF) for the primary prevention of HIV infection in certain settings. [1*] Nevertheless, there is interest in enhancing PrEP with: different

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dosing schedules; other oral agents; alternative modes of delivery (topical and injectable); and novel agents such as broadly neutralizing antibodies. Further, besides PrEP there are other effective means of preventing HIV infection, including treatment as prevention, voluntary medical male circumcision, and behavioral interventions. Assessing whether promising new interventions are safe and effective as well as determining optimal prevention strategies necessitates research. However, the growing armamentarium of prevention modalities introduces a complex array of practical, scientific and ethical challenges. After all, given the established safety and efficacy of particular modes of prevention, when and how is it ethically acceptable to test alternate approaches that will be scientifically informative? This review describes a range of considerations regarding how to answer this perennially difficult question in regard to the use of OPTF in future HIV prevention research.

Although somewhat intertwined, questions regarding the use of daily OPTF in research can initially be considered in two broad categories: use in a comparison arm (to something being evaluated in a trial) and as a standard of prevention (the prevention package made available to all participants in a trial). Each will be discussed in turn followed by some cross-cutting issues related to the use of OPTF in research.

Comparison Arm

There have been longstanding controversies about the selection of the comparison arm in HIV prevention research, beginning with the design of perinatal HIV transmission following the results of ACTG 076, which demonstrated the efficacy of azidothymidine (AZT) in this setting. The ACTG 076 regimen included oral AZT during pregnancy and intravenous AZT during labor and delivery. [2] However, it was infeasible to implement such a costly regimen in some resource limited settings that were facing extraordinarily high prevalence rates of HIV infection. For instance, programs for HIV counseling and testing were not widespread, precluding the identification of many HIV infections during pregnancy and thereby making the administration of oral antiretroviral agents unrealistic. In addition, deliveries were infrequent in facilities capable of providing intravenous therapies. Consequently, alternative regimens that focused simply on the provision of peripartum oral antiretroviral agents were proposed even though they were not expected to be as effective as the ACTG 076 regimen. Therefore, a placebo was typically selected as the comparator, which also promised to provide a clear answer regarding safety and efficacy more quickly than if an active arm was employed. This was especially important given the nature of the epidemic. Nonetheless, critics alleged that consistent with the contemporaneous version of the Declaration of Helsinki a placebo comparator arm was ethically unacceptable because the 076 regimen was known to be effective. [3] Ultimately, these approaches were shown to be effective, but concerns about appropriate comparators continue, especially placebo comparators, which are not limited to HIV prevention science. [4,5]

For example, the Declaration of Helsinki, includes a specific principle on placebos:

> “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

> Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
>
> Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
>
> Extreme care must be taken to avoid abuse of this option." [6]

The Council for International Organizations of Medical Sciences (CIOMS) also addresses comparators:

> As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment". Placebo may be used: when there is no established effective intervention; when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects." [7, p. 37]

Commentary following this guideline makes the important point that: "A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results. When the objective is to establish the effectiveness and safety of an investigational intervention, the use of a placebo control is often much more likely than that of an active control to produce a scientifically reliable result." [7, p. 38] A discussion follows about the appropriateness of particular comparator arms that depends in part on the nature of the disease or condition, currently known treatments, and the availability of the treatments in host countries.

Similarly, the International Conference on Harmonisation details some of the scientific tradeoffs associated with different design choices, offering an array of alternatives that should be considered. [8]

Ethics guidance directed specifically at biomedical HIV prevention trials was published by UNAIDS/WHO in 2007, which includes guidance regarding control groups:

> "Participants in both the control arm and the intervention arm should receive all established effective HIV risk reduction measures. The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been scientifically validated in comparable populations or approved by relevant authorities." [9, p. 51]

Commentary that follows focuses placebo controls, which was particularly salient at a time when there were limited trial data to support most HIV prevention efforts, except for

methods to decrease vertical transmission and voluntary medical male circumcision. Of note, a number of early trials of OPTF were done with placebo comparators consistent with this guidance.

The HIV Prevention Trials Network (HPTN) Ethics Guidance for Research that was revised in 2009 includes recommendations regarding the selection of a comparator arm under the more general heading of research design: “HPTN investigators will design HIV-prevention research capable of answering important research questions or producing valuable information while minimizing risks and maximizing benefits to study participants and their communities.” [10, p. 18] The commentary indicates that:

> HPTN requires the selection of control or comparison arms that reflect accepted practices in HIV prevention while concurrently permitting the generation of scientifically valid results and useful data. A prescriptive approach to designing control or comparison arms within HPTN is not feasible due to the complexity of the issue. However, following international norms on clinical equipoise, interventions tested in HIV prevention studies should generally be compared against known effective interventions, and any exceptions to this rule require stringent scientific and ethical justification. [10, p.18]

The commentary next provides a series of questions to be addressed during research development to help ensure that the control and comparison groups are appropriate:

- Are there other known effective interventions that could be feasibly implemented to achieve the same goal? Will the experimental intervention be evaluated relative to those interventions?
- Does the trial design preclude or limit the use of any known effective interventions that are or could be made readily available to research participants in the proposed research sites?
- Does the trial design assume that any known effective interventions will not be available at the proposed research sites?
- If other known effective interventions exist, is there evidence to suggest that the experimental intervention will be more efficacious, cost-effective, or socially appropriate to implement in the research communities should the research show the intervention to be meaningfully effective?
- Should the trial have blinded control groups to reduce potential bias or should it include unblinded arms to test effectiveness of the intervention in more real world circumstances?[10, p. 18]

Considering the current evidence regarding OPTF, Cowan and Macklin address its role in future HIV prevention research, basing their arguments primarily in the provisions of the UNAIDS guidance. [11**] Consequently, their discussion about the selection of the control arm focuses on the modality being evaluated and the nature of the study population. First, they conclude: “if the study aims to demonstrate efficacy of a product similar to oral PrEP, a placebo control could not be justified. This may include studies that test a new daily oral antiretroviral for PrEP; test a longer acting version of an antiretroviral already in use; or test

a new dosing strategy of an oral antiretroviral." [11**, p. 294] In contrast, "a nonoral mode of drug delivery sufficiently distinguishes such new products from oral PrEP, so the use of placebo could be justified." [11**, p. 294]

While it does seem generally inappropriate to use a placebo control when evaluating an intervention similar to OPTF, the acceptability of using a placebo control in evaluating *all* nonoral modes of drug delivery warrants additional scrutiny. For example, consider a late stage trial evaluating the efficacy of a new injectable form of PrEP in a population at high risk of HIV-infection. Here the use of a placebo control of the injectable agent could be critical in answering the clinically relevant research questions related to determining safety and efficacy, but research ethics also demands minimizing risks to the participants. Accordingly, the trial could use a "double dummy" design, providing all participants with an active agent, but also a placebo. That is participants would be assigned to either: 1) the active injectable agent and placebo OPTF; or 2) a placebo injectable agent and active OPTF. While the research questions underscore that there is an uncertain degree of protection that may be afforded to those in the experimental arm, ethically conducting such a trial assumes that there is sufficient evidence from prior research to suggest that protection is probable and that the potential benefits (e.g., by overcoming problems with adherence to OPTF that are related to effectiveness) counterbalance this risk. Accordingly, consistent with the HPTN guidance, this approach seems to provide protection of participants and positions the trial to answer clinically meaningful questions.

Second, Cowan and Macklin rightly argue, "[t]he burden of proof in this situation – that new populations to be studied are substantially different from those where TDF/FTC has been shown to be effective – should lie with those who would defend the use of placebo in future trials." [11**, p. 294].

Standard of Prevention

In contrast to the intervention and comparison arms in a trial, which are expected to differ, the standard of prevention generally refers to the package of prevention modalities available to all participants in a trial regardless of their treatment assignment. Traditionally the prevention package typically consisted of counseling, HIV testing, the provision of condoms, and testing and treatment for sexually transmitted infections. Subsequently, the provision or referral for voluntary medical male circumcision was provided in some contexts. However, the growing number of established methods of prevention militates towards a more robust prevention package in the interest of helping to ensure the well-being of participants. Nevertheless, this desire potentially abuts the competing goal of fielding a trial that is scientifically informative, which may be compromised if a large number of infections are averted due to uptake of the prevention package.

Akin to the debates associated with determining the comparison arm in trials, establishing the appropriate prevention package has also been contentious. At one extreme, UNAIDS requires

> "that appropriate counselling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV

> prevention trial. New HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities." [9, p. 45].

However, a stakeholder engagement exercise that followed promulgation of these guidelines offered few areas of consensus in the abstract, but did develop a series of questions that could be employed by key stakeholders faced with making decisions about standards of prevention. [12]

The HPTN Ethics Guidance Document takes a more limited approach to the standard of prevention than that articulated by UNAIDS. Here, whether a particular preventive intervention should be included in a prevention package requires considering whether it is: 1) effective; 2) reasonably accessible; and 3) practically achievable. [13] Such assessments should be guided by scientific findings and community engagement. Determining if a particular method is 'effective' is based on sound scientific data and there should be "no reasonable basis for questioning the effectiveness of the method in the local research setting." Being 'reasonably accessible' "indicates that the services are free or at a cost within the means of research participants, can be implemented safely and legally within the research participants' community, and if no other significant obstacles to access exist, can be reasonably overcome by efforts of investigators and the CAB [Community Advisory Board]." 'Practically achievable' "means the service could reasonably be implemented and sustained in the community independent of the resources and infrastructure required for the conduct of the trial." [10, p. 32] Of note, while providing a prevention package is an ethical obligation, the content of the package is an ethical aspiration.

When addressing whether OPTF in particular should be considered as a standard of prevention, Cowan and Macklin examine the three considerations distilled from the relevant UNAIDS guidance point ('scientific validation', 'approval by relevant authorities' and 'consultation among stakeholders'), concluding that OPTF should be part of the prevention package in future prevention trials. [11**] Whether their conclusion is warranted requires examining their arguments.

First, while the preponderance of data supports including OPTF as a standard of prevention, careful attention must focus on whether this remains true in any particular setting as suggested in the HPTN guidance.

Second, Cowan and Macklin dismiss the relevance of the UNAIDS criterion for local approvals since this may pose a substantial barrier to implementing OPTF in the prevention package in some settings. While at first glance the global data regarding safety and efficacy of OPTF suggest that failing to include it in the prevention package could likely place at least some participants at undue risk, it is also important to consider the role of drug registrations and approval in ensuring the safe and appropriate use of agents. Accordingly, the reasons for the lack of approval should be considered. For instance, approval may have been withheld due to profoundly low rates of adherence in trials in a particular setting or there may be the absence of an appropriate infrastructure to implement OPTF, both of which could pose considerable risks and constitute reasonable reasons for decisions regarding approval in some settings. In contrast, lack of approval may be due primarily to market

considerations that do not alone provide sufficient justification for excluding OPTF from the control arm. Therefore, whether OPTF is approved locally may be important not only in terms of safety, but also whether it can be legally and practically implemented as underscored in the HPTN ethics guidance.

Third, Cowan and Macklin presuppose the results of stakeholder engagement. However, the interests and priorities of stakeholders are likely to differ depending upon context. Further, the process of stakeholder engagement itself is a critical aspect of determining the appropriate standard of prevention since it should capture the preferences and interests of those most affected by it. [14]

Cross-Cutting Issues

Additional issues to consider regarding OPTF in research that bridge concerns relate to the comparison arm and the standard of prevention are acceptability, adherence and washout phases with long-acting products.

Acceptability. The acceptability of OPTF to particular individuals and communities should be considered in determining whether it is ethically appropriate to use in a particular trial. While substantial data now support the use of OPTF, uptake is variable among those at risk of infection. There are many plausible reasons for low uptake, including lack of knowledge, cost, local availability, hesitation to medicalize sexuality, and stigma associated with use. While some of these issues (e.g., knowledge) could be overcome for research, others (e.g., stigma) would not. Accordingly, it is essential to determine the acceptability of OPTF for the proposed study population in light of any structural and cultural barriers to use. An area that warrants further consideration is the extent to which certain aspects of acceptability ought to properly weigh into design decisions. For instance, if certain individuals at high risk of infection were disinclined to use OPTF despite its availability, would it be appropriate to include them in a trial of a topical or novel agent with a placebo comparator? In evaluating a design question such as this, it will be important to assess the rationale for such decisions and that they are based on a true understanding of the nature of OPTF. The extent to which the results of such a study will be generalizable also necessitates deliberation. Of note, such an option would not be appropriate for the evaluation of a long-acting injectable agent where an oral run-in assessment for safety would necessitate the use of oral PrEP with the analog of that agent.

Adherence. Clinical trial data underscore the importance of adherence in the efficacy and safety of OPTF. Accordingly, an important set of practical and ethical questions emerge regarding what efforts will be taken regarding adherence to OPTF in research. For example, when should OPTF be permitted, provided, and/or promoted and to what extent? In the case of an efficacy trial where OPTF is used as the comparator, clearly OPTF should be provided and vigorously promoted. However, in later stage effectiveness research, the extent of promotion should arguably approximate that which is scalable following the trial. Further, when OPTF is considered to be part of the prevention package, there may not necessarily need to be a responsibility to provide OPTF, but rather to ensure access to it.[8] Given these complexities, deliberating about these issues as trials are being designed is essential since

they are poised to have considerable impact on trial integrity and the well-being of participants.

Washout and Long-Acting Agents. When designing and implementing trials of new long-acting agents such as an injectable agent in high risk populations, it is important to consider the need to supplement the prevention package with the use of OPTF following the administration of the final dose of study product to protect participants during this period when antiretroviral activity will be waning. After all, having lower levels of an active agent would not only heighten the risk of infection, but also of the risk of developing resistance. Accordingly, in this context, the active provision of OPTF accompanied by aggressive promotion is essential.

Conclusion

Reflecting on debates regarding the selection of the comparator arm and the standard of prevention, Dawson and Zwerski recently identified four key considerations in determining ethical acceptability in HIV prevention research: scientific viability, participant and community welfare, trial efficiency, and trial usefulness for decision making. [15] While this framework outlines some necessary considerations for determining whether OPTF should be included in a trial, based on the observations above it is arguably insufficient. At minimum, this framework will need to be supplemented by 1) concern for the autonomous preferences of individuals regarding the acceptability of particular methods of prevention; 2) procedural justice to capture fair processes for decision making [16]; and 3) social justice [17].

In summary, although the preponderance of evidence poses a rebuttable presumption for the use of OPTF as a comparator or as part of the standard of prevention in future research, it will be essential to develop ordered ways of supporting or rebutting this presumption for particular trials. Doing so will be optimized by robust stakeholder engagement taking into account scientific considerations, the modality being evaluated, acceptability, adherence and the local context. Consideration should be given to requiring an explicit attention to these decisions and how they were made in protocols and publications.

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Key Points

- Although substantial evidence supports oral pre-exposure prophylaxis with tenofovir disoproxil fumarate and emtricitabine for the primary prevention of HIV infection in certain settings, research is needed to assess promising HIV prevention interventions.
- While there is arguably a rebuttable presumption for the use of oral PrEP as a comparator or as part of the standard of prevention in much future HIV prevention research this needs to be assessed for a particular trial.
- Determining the ethically appropriate comparator and the standard of prevention for a trial necessitates obtaining robust stakeholder engagement that takes into account scientific considerations, the modality being evaluated, acceptability, adherence and the local context.