Trials of Intermittent Dosing of Pre-Exposure Prophylaxis (PrEP)

Preparing for PrEP: Policy, Practice and Politics

Summary from the AVAC Think Tank

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Executive Summary

Colleagues from multiple agencies and research disciplines participated in a one-day meeting to identify key scientific questions to be addressed in evaluating the merits of future prevention research on intermittent use of pre-exposure prophylaxis ("iPrEP") for prevention of HIV. The objectives of this consultative meeting were to:

- Provide an update on current PrEP effectiveness trials.
- Assess the scientific and operational issues raised by an intermittent use PrEP effectiveness trial.
- Identify next steps in the intermittent use PrEP research agenda in light of information presented at the meeting.

The following recommendations and observations were identified:

- Multiple definitions exist of what constitutes "intermittent" and whether it would be fixed-dose or exposure-dependent or a combination.
- Non-human primate research supports iPrEP but does not adequately inform intermittent dosing in humans.
- The optimal dosing strategy for an intermittent dosing trial remains a matter of debate.
- An intermittent dosing trial could provide insight into the utility of dosing schedules and adherence.
- No identifiable funding source exists at present for an intermittent dosing effectiveness trial.
- For some, but not all participants, a placebo-controlled intermittent dosing effectiveness trial is not the most critical priority for the PrEP research agenda at this point in time.
- A non-inferiority trial testing daily vs. intermittent use is likely to be impractical due to the size of the trial necessary to test this hypothesis.
- Ongoing and planned daily dosing trials could provide valuable information to indirectly assess the effect of intermittent dosing.
- Comprehensive samples should be collected from ongoing and planned daily dosing trials to permit the necessary pharmacokinetic, pharmacodynamic and

phosphorylation analyses to develop surrogate markers for prevention of HIV infection.
- The iPrEP scientific agenda would benefit from testing other PrEP agents in addition to TDF and TDF/FTC.

Background

The meeting began with presentations on the current status of the PrEP trials under consideration, in planning or in progress testing the effectiveness of antiretrovirals to prevent HIV infection, or reducing viral load post infection. Current PrEP trials include phase II and III placebo-controlled randomized trials to test the safety and effectiveness of daily oral tenofovir (TDF) or TDF combined with emitricitabine (FTC). All of these trials test daily oral antiretroviral use. There were also presentations on the results from recent non-human primate (NHP) trials testing both topical and oral PrEP. After the presentations, the group discussed the specific meeting objectives:

- Assessing the scientific and operational issues raised by an intermittent use PrEP effectiveness trial.
- Identifying next steps in the intermittent use PrEP research agenda in light of information presented at the meeting.

Roundtable Discussion

The discussion began with the proposition that each of the current daily dosing trials may deliver a crude indication of the effect of intermittent dosing given the likelihood of incomplete adherence to the daily recommendation of the protocol. Indirectly, the field may learn about the effect of intermittent use from the current trials due to improper adherence.

However, it was agreed that incomplete adherence could not be considered structured intermittent dosing and usage will vary. Some participants questioned whether varying adherence could, in fact, provide scientifically valid insights.

There was consensus that blood levels, combined with the possibility of hair analysis could provide useful indicators of adherence. The practicality and utility of measuring drug levels in blood during these trials was discussed. However, there was concern that given the long half-lives of TDF and TDF/FTC, researchers may not be able to extrapolate adherence rates with accuracy.

There was discussion of whether PrEP effectiveness was likely to require daily dosing. There is an extended window of protection by the PrEP dose likely due to long intracellular drug half-lives. NHP studies also suggest that daily gel or oral dosing is not necessary for high protection. NHP studies were thought to be useful in helping to address questions about intermittent vs. daily use, optimal delivery modality, dose exposure effect and pharmacokinetics and pharmacodynamics.

The PrEP field faces sampling challenges. The current trials lack consistent intracellular data, or data on tissue concentration. A key question for the PrEP field is what is the optimal range where you achieve sufficient protection without unacceptable toxicity?

The group discussed how intermittent dosing strategies might affect resistance. With a single drug, resistance can be established. The route of administration will also affect resistance. At higher levels of effectiveness, there is lower potential for resistance to develop. The greatest driver of resistance is inadvertent use of PrEP by individuals who are infected but not diagnosed, highlighting the need for scaled-up testing service linked to PrEP, whether daily or intermittent.

A discussion on adherence and dosing noted that adherence is the "Achilles heel" of PrEP. Adherence issues may remain regardless of the type of trial, in as much as changing the dosing regimen may not impact adherence.

The group opened up the discussion to address the questions whether it is advisable to start an intermittent dosing trial before we have results of a daily trial. There is some concern that the window to proceed with an intermittent trial may be rapidly closing. It was questioned whether once results for daily use from one of the current trials are available whether it will be possible to ethically test intermittent use in a placebo controlled trial? An intermittent trial in these circumstances might no longer be feasible.

The group also discussed the feasibility of a non-inferiority trial. The challenges of non-inferiority trials were seen as further evidence of the need to establish surrogates of HIV protection. The issue was raised of the importance of examining how margins are estimated in non-inferiority trials. Greater coordination to combine data to establish smaller margins for these studies was suggested.

There was a discussion of what kind of intermittent trial should be given priority. Some participants expressed the view that the case for studying intermittent dosing in efficacy trials had yet to be made. The cost of such a trial was also discussed. What if the daily dosing studies show only 50% effectiveness? Will an intermittent dosage trial still be relevant? There were also questions about whether any country would be able or willing to adopt daily use without considering the possibility of intermittent usage.

Dose optimization in the current trials was questioned, and it was agreed that the dosing had been based upon what had been proven as effective treatment. There was support for, and a greater call for, researchers to undertake further adherence and behavioral studies.

There was also a clear and urgent call to collect and understand samples and information from existing studies and to build this into the design of future trials.

The group then discussed if there was sufficient equipoise to justify an intermittent trial. A trial would need to have three arms: placebo, daily PrEP and intermittent PrEP. Some participants considered this to be better than a non-inferiority trial. There was general consensus that a Phase I or Phase II study to test safety, pharmacokinetics and adherence of intermittent dosing strategies may be more useful and practical to deliver than a large non-inferiority efficacy trial.

Given the knowledge to date and discussions, the group agreed that there were three possible scenarios for taking intermittent PrEP forward:

1. Do a study (or multiple studies) testing intermittent dosing strategies.
2. Undertake smaller trials to answer adherence questions.
3. Wait for more data from current daily studies.

There was agreement that the field has limited resources, and that other agents have yet to be brought into the equation. There was also agreement that issues such as pharmacokinetics, drug resistance and adherence need to be studied more closely from current and planned trials.

Conclusions

While not unanimous, a tentative consensus did emerge:

1. Undertaking a placebo-controlled intermittent effectiveness trial may not be the top priority at present, and may not be feasible due to the reluctance of funders to initiate such a study.
2. Better data collection from current trials was urgently needed to establish better surrogate markers and correlates of protection.
3. Small intermittent trials could begin to help answer some questions related to adherence and behavior.
4. A comprehensive PrEP research plan is needed that prioritizes next steps in terms of dosing, other agents, other populations and long-term effects.

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