Consultation on the Intermittent PrEP (iPrEP) Research Agenda
Summary of a think tank sponsored by amfAR and AVAC

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Multiple clinical trials are now testing the safety and efficacy of oral pre-exposure prophylaxis (PrEP) as an HIV prevention intervention. Nearly all of these trials are testing a once-daily regimen of tenofovir disoproxil fumarate (TDF) or TDF plus emtricitabine (FTC). Initial safety and efficacy data from these trials will be available as early as the third-quarter of 2010. While the first results will come from trials of once-daily dosing, there is considerable interest in intermittent use of PrEP (iPrEP). iPrEP is being considered for a number of reasons: exposure to HIV is typically intermittent; intermittent use of PrEP has been found to be protective in non-human primate models; iPrEP may be more cost-effective than daily use; and intermittent use may lead to different levels of side effects, toxicity and adherence. As of this writing, two small safety and adherence trials of iPrEP are underway. Two additional trials, one assessing behavior, another assessing pharmacokinetics (PK) and pharmacodynamics (PD) will being enrolling soon. (See Table 1 below for details about these ongoing and planned oral PrEP studies.)

Meeting objectives

In December 2009, AVAC and amfAR convened a one-day meeting of leaders from research and research sponsor agencies to review the status of biomedical, behavioral and animal research relevant to iPrEP, identify gaps in this research, and suggest priorities for moving forward. Objectives of this meeting were to:

- Provide an overview of current PrEP clinical research and animal studies.
- Review current and planned iPrEP studies and behavioral research (including pill-taking (adherence) and risk behavior, and sexual practices of MSM and other populations).
- Consider what more the field needs to learn from current and planned research; what additional behavioral and biomedical research is needed; and how to make the iPrEP research agenda appropriately focused, evidence-based and as comprehensive as possible.

Meeting summary

Overview of current PrEP clinical research and animal studies

Current studies are testing oral PrEP in a variety of populations and geographic settings, though these studies are limited in the range of drugs being tested (all large-scale trials are testing oral TDF or TDF/FTC). This year nearly 20,000 individuals will be enrolled in PrEP trials. Most of the current efficacy trials are powered to assess whether PrEP has efficacy in the 50% - 70% range. (There are also studies of a topical ARV-based microbicide gel that includes tenofovir. Topical and oral ARV-based prevention research face many similar issues, but this meeting focused specifically on oral PrEP.)

There have been a variety of PrEP animal studies, assessing both daily and intermittent regimens, via different routes of transmission and with different levels of virus exposure. Animal studies to date suggest that:

- Higher drug levels in the blood are more protective.
- Combination TDF/FTC appears to be more protective than TDF alone (the former was protective against infection while the latter delayed infection in a low-dose challenge model).
- A post-exposure dose is important for protection.
- FTC quickly penetrates rectal tissue and TDF persists for extensive time periods.
- A pre- and post-exposure TDF/FTC regimen appears to be effective against $SHIV_{162p3}$ containing the M184V mutation in the reverse transcriptase gene (a monkey version of HIV that is resistant to FTC).

Table 1: Current and planned iPrEP studies and behavioral research

Study	iPrEP Regimen(s)	Study question(s)	Location(s)/ Timing	# participants/ population(s)
Ongoing				
IAVI E001	TDF/FTC, one tablet Monday and Friday and again within 2hrs of sex, not to exceed one dose per day	Primary endpoints: ▪ Safety of daily and intermittent TDF/FTC ▪ Compare acceptability and adherence ▪ Evaluate mean intracellular drug levels ▪ Evaluate relationship between adherence and intracellular drug level ▪ Evaluate changes in HIV-associated risk behavior Exploratory ▪ HIV-specific immune responses in volunteers randomized to TDF/FTC and placebo (no mucosal sampling in study)	Kenya Start: Q3 2009 End: Q2 2010	72 / MSM and FSW
IAVI E002			Uganda Start: Q3 2009 End: Q4 2010	72 / serodiscordant couples
Planned				
HPTN 066	Oral TDF/FTC directly observed regimens: ▪ 1 tablet once weekly ▪ 1 tablet twice weekly ▪ 2 tablets twice weekly ▪ 1 tablet daily	Primary objectives: ▪ Demonstrate dose-proportionality of intracellular TFV-DP and FTC-TP from weekly to daily dosing in PBMCs ▪ Describe intra-individual variability in intracellular TFV-DP and FTC-TP concentrations at steady-state (comparison of Day 28 and Day 35) in PBMCs Secondary objectives: ▪ Describe the relationship between pre-dose and decaying concentrations of TFV, FTC, TFV-DP, FTC-TP and Day 35 and Day 49 in blood serum, PBMCs, CD4+ blood cells, tissues cells (unselected) and CD4+ tissue cells, tissue homogenate and luminal fluid at steady state ▪ Describe differences in intracellular TFV-DP and FTC-TP steady-state concentrations in men and women ▪ Characterize the safety profiles of four different TDF/FTC PrEP regimens	US Start: Q3 2010 End: Q1 2011	32 / men and women

Study	iPrEP Regimen(s)	Study question(s)	Location(s)/ Timing	# participants/ population(s)
HPTN 067	Oral TDF/FTC ▪ 1 tablet daily ▪ 1 tablet twice weekly plus after 1 tablet after sex ▪ 1 tablet before sex and 1 tablet after sex	Primary objectives: ▪ Adherence, with hypothesis that non-daily usage may yield: - No less coverage of exposure - Increased adherence - Decreased symptoms - Decreased pill costs Secondary objectives: ▪ Usage pattern preference ▪ Social roles ▪ Drug exposure	Select African countries to be determined, Thailand Start: TBD End: TBD	360 / women and MSM
HPTN – HIV Prevention Trials Network; IAVI – International AIDS Vaccine Initiative; TDF – tenofovir disoproxil fumarate; FTC – emtricitabine				

Behavioral research, pill taking, sexual behavior and adherence

Establishing patterns of sexual exposure will be critical to understanding the potential for intermittent PrEP usage. There has been a great deal of research on the sexual behavior of different populations affected by HIV/AIDS, but only a very limited body of research has explored issues such as sex frequency, spacing and planning among populations at elevated risk for HIV. This kind of data will be valuable in helping to inform which PrEP modalities might be most effective for various populations.

The Bangkok MSM Cohort Study is examining HIV incidence, and sex frequency, spacing, and planning, and the factors that affect each of these variables (e.g., alcohol use, getting paid for sex). The data collected from the study thus far have suggested that:

- Most men were exposed to HIV infection only intermittently.
- Most men had a window of opportunity to take a pre-exposure dose.
- Correlates of more frequent sex were alcohol, drugs, group sex, sex with foreigners and engaging in commercial sex.
- Correlates of unplanned sex were younger age, lower education, not identifying as gay, receptive role in anal sex and not engaging in group sex.

Objective measures of adherence are important to understanding whether intermittent dosing may improve adherence compared to daily dosing. Current trials are recording sexual histories and gathering other behavioral data using a variety of methods, including computer-assisted self interviews (ICASI), sexual behavior timelines, and data collection via SMS. Strategies for measuring adherence currently in use in clinical trials include unannounced pill counts, MEMS caps and real-time wireless adherence monitoring systems (Wisepill wireless monitoring).

There was discussion of the lessons learned from Post-Exposure Prophylaxis (PEP) in terms of messaging, roll out and adherence. Data from a study of Fenway Health's NPEP program indicated low completion rates among PEP recipients, but PEP distribution also provided a "teachable moment" and risk behaviors went down with PEP and counseling. Other studies of NPEP have shown similar results. Conclusions of these studies include:

- PEP administration is feasible, but labor intensive in a community-based setting.
- Utilization has been limited by "ambivalent" social marketing campaigns, e.g. "PEP is available but we don't want you to have to use it"
- Using PEP does not necessarily change risk taking behavior.
- Active mental health and substance use counseling is important.

A number of studies regarding knowledge of and interest in PrEP make it clear that context matters: perceived side effects, efficacy, cost, and dosing flexibility all affect interest in using PrEP.

What do we need to learn from current and planned PrEP trials?

It is hoped that the ongoing and planned PrEP trials, testing both daily and intermittent use, provide information in a variety of areas that can inform further PrEP and iPrEP research, including:

- Determining whether daily PrEP works to lower the risk of HIV infection;
- Data on whether PrEP drugs are reaching appropriate sites in the body rapidly enough to block infection (e.g., mucosal sites in the case of sexual exposure);
- Greater understanding of both sexual and pill taking behavior;
- Greater understanding of breakthrough infections across studies;
- Greater understanding of correlations between exposure, protection and drug levels in blood and other compartments.

Current clinical trials may not provide definitive information that correlates drug levels in the blood with HIV protection, if there is protection. Blood samples are typically taken only every three months and it is difficult to know when an individual was exposed to HIV and what his or her drug levels were at the time. Positive results from current PrEP trials may lead some to conclude that a clear threshold for protection has been determined, but that will not necessarily be the case.

The Bill & Melinda Gates Foundation is working in partnership with others to address a variety of issues that were raised during the meeting, including improved data sharing and standardization studies, and planning for possible PrEP delivery.

Priorities for advancing PrEP and iPrEP research

There was not a consensus about the appropriateness of launching iPrEP efficacy trials in the near future, particularly in advance of results from current clinical trials of daily PrEP. However, a variety of priorities for advancing iPrEP research raised during the day appeared to have broad support. Major themes included the need for:

- **Additional behavioral research and closer links between behavioral and biomedical research related to iPrEP:** More behavioral research is needed to better understand the potential for effective intermittent use of PrEP, as well as optimal dosing schedules and adherence across a range of populations and geographic settings. Priority research topics include sexual frequency, patterns, and planning; risk behavior, and the role of sex in people's lives. Expanded research is also needed on adherence and pill-taking practices. Attention is needed for developing objective

adherence measures and metrics for adherence and to use of electronic monitoring of adherence.

- **Standardization and collaboration**: Standardization of drug adherence and drug exposure measures would greatly assist interpretation of current and future trial results. Standardized techniques to measure pharmacokinetics (PK) and pharmacodynamics (PD) are needed, as are streamlined protocols for saving cells. Research organizations should work collaboratively to establish standardized measures in these and other areas.
- **Doing more to collect and mine data**: More comprehensive collection of samples from current and planned trials is needed to perform PK, PD and phosphorylation analyses that may identify surrogate markers for protection. In addition, the PK and PD data on existing drugs can be reviewed to determine how different drug classes access human cells, helping us to understand which drugs may be effective at the site of exposure.
- **Additional resources for iPrEP studies:** At least one planned iPrEP clinical trial scaled back enrollment plans due to lack of resources. Conversations during the day identified the opportunity to learn more about the potential for iPrEP through expanded animal research and a range human studies in the areas of adherence, acceptability, behavior, safety and perhaps efficacy.
- **Planning for results:** Before results from current trials are available, the field should work towards agreement on the parameters for data evaluation (e.g., per protocol v. intent-to-treat) and clear communication of results. It is worth considering different scenarios and timelines for results of once-daily and intermittent PrEP studies, and their impact on each other.
- **Planning for implementation:** More modeling of PrEP delivery is needed to understand delivery models that can achieve the greatest public health impacts in different settings. Social marketing studies can be initiated now. Current clinical studies will provide some information on acceptability, but additional research is needed in this area to understand preferences across multiple populations. Post-marketing research will be needed for adherence, risk perception and risk taking that will have important implications on PrEP implementation generally and on intermittent PrEP specifically.

PrEP, whether used daily or intermittently, may prove ineffective. Or, it may turn out to be a unique and important new opportunity to reduce HIV infection and change the course of the epidemic. People at risk of contracting HIV cannot afford to let biomedical and behavioral PrEP research be delayed unnecessarily. 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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