Pre-Exposure Prophylaxis (PrEP)

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What is PrEP?

Pre-exposure prophylaxis, or PrEP, is a strategy that involves use of antiretroviral medications (ARVs) to reduce the risk of HIV infection via sexual exposure. All of the current effectiveness and follow-on trials are testing tenofovir-based regimens—using either TDF/FTC (an antiretroviral containing tenofovir (TDF) and emtricitabine (FTC) that is sold under the brand name Truvada) or TDF (an antiretroviral pill marketed under the brand name Viread). *Based on the data that have been collected to date the US Food and Drug Administration (FDA) announced its approval of daily oral TDF/FTC for PrEP in 2012.*

What are the data from efficacy trials of tenofovir-based PrEP[1]?

To date, four trials have found evidence of HIV prevention benefit using tenofovir-based PrEP:[2]

- The multi-country iPrEx trial showed that once-daily oral TDF/FTC reduced risk of HIV by 42 percent overall in gay men and transgender women.
- The Partners PrEP trial discontinued the placebo arm of the study after an interim review of trial data by its independent data and safety monitoring board (DSMB) showed that both once-daily oral TDF/FTC and once-daily oral TDF are effective at reducing risk of HIV infection for the HIV-negative partner in the heterosexual HIV-serodiscordant couples enrolled in the trial (one partner is HIV-negative and one HIV-positive)—TDF/FTC by 75 percent overall and TDF by 67 percent overall.
- The TDF2 trial in heterosexual men and women in Botswana showed that once-daily oral TDF/FTC reduced risk of HIV infection by 63 percent overall.
- The Bangkok Tenofovir Study found that daily oral TDF reduced risk of HIV infection by 49 percent in injecting drug users.

To date, two trials have found no evidence of benefit using tenofovir-based PrEP:

- FEM-PrEP, which evaluated once-daily oral TDF/FTC in women in east and southern Africa found that while the product was safe, there was no evidence of benefit and halted early based on a recommendation from the trial's independent DSMB. In early 2012, the FEM-PrEP trial team presented analysis suggesting that, in FEM-PrEP, low levels of adherence could explain the trial outcome.
- VOICE was a five-arm trial of once-daily oral TDF/FTC, once-daily oral TDF and daily 1% tenofovir gel. The oral TDF and gel arms were stopped early after interim DSMB reviews in 2011 found the interventions to be safe but not effective in the study population. In March 2013, results from all three arms were presented. Data showed that none of three interventions tested in VOICE provided additional protection against HIV in the study, likely because few of the women in the trial used the products as directed.

Follow-up research is ongoing to learn more about the results in all of the trials described above:

- The iPrEx Open-Label Extension (iPrEx OLE) study provides daily TDF/FTC to HIV-negative iPrEx trial participants in the context of less intensive monitoring and follow-up. This trial has completed enrollment. Results from data analysis may be available in 2014.
- TDF2 is planning a follow-on trial of once-daily oral TDF/FTC in men and women that will learn more about the effect of the intervention in the context of less intensive real-world monitoring.
- VOICE and FEM-PrEP trial teams are continuing to analyze data on adherence, risk behavior and other factors that might have affected the effectiveness of TDF and TDF/FTC, respectively. A peer-reviewed publication with data from FEM-PrEP was released in July 2012.
- The Bangkok Tenofovir Study is continuing to provide daily TDF to HIV-negative participants as part of a one-year follow-on trial to assess real-world efficacy.

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[1] Please visit *www.avac.org/prep* and *www.avac.org/pxrd* for up-to-date timelines tracking ongoing research.

[2] All of the safety and effectiveness trials described here offered participants PrEP or an identical placebo pill plus a standard prevention package. For more on HIV prevention trial design and standard of prevention see *www.avac.org/trials*.

A range of additional trials are ongoing including research on intermittent, less-frequent dosing strategies (all of the efficacy trials to date evaluated once-daily regimens) and other medications. For a comprehensive review of completed and ongoing PrEP trials, visit http://data.avac.org.

What are some key developments or conclusions from PrEP effectiveness trials so far?

- There were no significant side effects observed in trials of tenofovir-based PrEP in any of the trials.
- Adherence is essential. Each of the trials that found benefit also found that people who had high levels of adherence had high levels of protection. Lower adherence was associated with low or no protection.
- HIV drug resistance to PrEP medications was observed in some trials, but primarily in participants who were HIV-positive and in the "window period" of early infection when they began taking PrEP. These individuals tested HIV-negative on the trials' screening tests. This reinforces the importance of regular testing for anyone initiating or taking PrEP.
- TDF/FTC and TDF are both key drugs for treating HIV in HIV-positive people. Access to tenofovir-based PrEP can only be explored in the context of sustained ART access for HIV-positive people worldwide.

What is happening now?

Regulatory and guidance activities: In July 2012 the US FDA announced its approval of daily oral TDF/FTC as PrEP. Also in July 2012, the WHO released guidance on PrEP for serodiscordant couples, MSM and transgender women in the context of demonstration projects. This research could lead to additional PrEP-specific programming guidance in 2015. Comprehensive guidance on ARV use—for both treatment and prevention—is currently in development by WHO and scheduled for release in July 2013. The US CDC is developing US Public Health Service (PHS) guidelines for the use of TDF/FTC as PrEP, which are expected in 2013. These will update the interim guidance documents on PrEP in gay men and other MSM, heterosexual adults at risk via sexual exposure and injecting drug users. The Southern African HIV Clinicians Society issued guidance in June 2012 for use of TDF/FTC as PrEP in gay men and other MSM. The European Medicines Agency (Europe's regulatory body) is updating its concept paper on the development of medicines to prevent HIV infection. Some groups have chosen a slower approach. The British HIV Association and the British Association for Sexual Health and HIV have stated that, based on available data, PrEP should only be prescribed in the context of a clinical trial until more data are available.

Demonstration Projects: Much more needs to be learned about the safety and effectiveness of PrEP in the real world. Demonstration projects are designed to gather information on safety, efficacy and program design for new interventions. They help guide subsequent larger-scale introduction. Such projects are planned or underway for the India, Kenya, Nigeria, Uganda and the US. For a list of ongoing demonstration projects visit http://www.avac.org/ht/a/GetDocumentAction/i/49807.

What is in the PrEP pipeline?

NEXT-PrEP (HPTN 069) is a recently launched Phase II safety and tolerability study comparing oral Maraviroc (MVC) alone, MVC/FTC, MVC/TDF and TDF/FTC for PrEP amongst men who have sex with men in the US. Next-generation strategies will use longer-acting drugs, focusing on those that are not widely used for HIV treatment. These include TMC278LA formulated as a long-acting injectable, a vaginal ring containing dapivirine and a vaginal ring combining dapivirine and maraviroc.

Priorities for 2013

As described in *AVAC Report 2012*, one of the priorities in 2013 is to define and roll out needed PrEP demonstration projects, which can provide much-needed information on how to identify those at risk who can benefit from PrEP and come up with programs that facilitate its safe and effective use. AVAC is working with advocacy partners in the US and internationally to push national health agencies to prioritize this work. This includes a statement released in March from a coalition of HIV and women's health advocates calling on US agencies to coordinate a PrEP agenda to quickly and accurately answer questions about how PrEP can be made available to women in the US. This builds on prior work on trying to define the demonstration project agenda for a range of populations, released before FDA approval.

For more resources on HIV prevention research and for information on AVAC programs, visit www.avac.org.