Pre-Exposure Prophylaxis (PrEP)

Additional information on PrEP is available at www.avac.org/prep. Interested in getting involved in PrEP advocacy? Email us at *avac@avac.org*.

What is PrEP?

Pre-exposure prophylaxis, or PrEP, is a strategy that uses antiretroviral medications (ARVs) to reduce the risk of HIV infection in HIV-negative people. 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).

What is the status of tenofovir-based PrEP research?

To date, three trials have found evidence of HIV prevention benefit using tenofovir-based PrEP:[1]

- 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 73 percent overall and TDF by 62 percent overall. The trial is ongoing in Kenya and Uganda.
- 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.

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 no evidence of benefit and halted early, after an independent Data Safety and Monitoring Board (DSMB) determined that while the product was safe, there was no possibility that TDF/FTC would reduce HIV risk in the context of the trial.
- VOICE, which was launched to evaluate once-daily oral TDF/FTC, once-daily oral TDF and daily 1% tenofovir gel halted its TDF arm after its independent DSMB determined that while the product was safe, there was no possibility that TDF would reduce HIV risk in the context of the trial. The 1% tenofovir gel arm was halted for the same reason. The TDF/FTC arm is ongoing.

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

- The iPrEx trial team has launched the iPrEx Open-Label Extension (iPrEx OLE) study, which will provide daily TDF/FTC to HIV-negative iPrEx trial participants in the context of less intensive monitoring and follow-up.
- The Partners PrEP trial has randomized all HIV-negative placebo recipients who gave informed consent to receive either TDF/FTC or TDF—and will continue to collect safety and effectiveness data on these two PrEP strategies.
- TDF2 is planning a follow-on trial of once-daily oral TDF/FTC in men and women, scheduled to begin enrolling in the first quarter of 2012. Like iPrEx OLE, this trial is designed to learn more about the effect of the intervention in the context of less intensive "real-world" monitoring.
- VOICE and FEM-PrEP trial teams are analyzing data on adherence, risk behavior and other factors that might have affected the effectiveness of TDF and TDF/FTC, respectively. Data from FEM-PrEP is expected in early 2012 while VOICE data is anticipated in 2013.

There are additional trials that have examined safety in many populations; and an ongoing efficacy study in injection drug users in Thailand. The French research agency ANRS has launched the pilot phase of a trial looking at the efficacy of an "on demand" dosing strategy, in which gay men and other men who have sex with men (MSM) would be counseled to use TDF/FTC daily during periods of sexual activity.

For a comprehensive review of completed and ongoing PrEP trials, visit www.avac.org/trials/prep.

[1] 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*.

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.
- Once-daily oral TDF/FTC reduces risk of HIV infection among gay men and transgender women, and both once-daily oral TDF/FTC and once-daily oral TDF reduce risk in heterosexual men and women primarily reporting penile-vaginal sex.
- Gilead Sciences, the manufacturer of Truvada (TDF/FTC) has submitted a dossier to the US Food and Drug Administration (FDA) seeking approval for a label change that would indicate that once-daily oral TDF/FTC can reduce the risk of HIV infection for HIV-negative adults.
- Adherence is essential. Each of the trials that found benefit also found that increased adherence was linked to increased protection. Evidence that an individual had taken the pill—e.g., self-report or detectable drug in the blood—was strongly predictive of protection.
- Where the data are contradictory—e.g., tenofovir-based PrEP in women—we don't have an explanation for the differences observed. Possible factors could include: adherence, interactions with hormonal contraceptives or other drugs, biological factors of the women and/or their partners and many others. We hope to learn more as each trial conducts further detailed analyses.
- Each of these trials was conducted in a highly controlled clinical setting. There is much more that needs to be learned about the safety and effectiveness of PrEP in the "real world".
- 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 December 2011, Gilead Sciences submitted a research dossier to the US Food and Drug Administration requesting an indication that Truvada (TDF/FTC) reduces the risk of HIV infection in HIV-negative adults. If it is approved, this would be the first HIV drug approved for use as an HIV prevention strategy. The submission is based primarily on the positive results from the iPrEx and Partners PrEP studies. A label change could affect a number of things, including: how widely TDF/FTC as PrEP is covered by insurance and/or public payers like Medicaid; whether there is specific monitoring and guidance on its use and public informational campaigns, among other things. In January 2011 the US Centers for Disease Control and Prevention (CDC) issued guidelines for health providers about TDF/FTC as PrEP in men who have sex with men (MSM). CDC is developing US Public Health Service (PHS) guidelines for the use of TDF/FTC as PrEP. The European Medicines Agency (Europe's regulatory body) published a concept paper on the development of medicines to prevent HIV infection in early 2011. It has also held a stakeholder consultation. Details on potential plans the EMA may have regarding guidance around PrEP are not available at this time. The World Health Organization (WHO) is convening an ad hoc advisory group to make recommendations that will inform WHO in its development of guidance related to the use of ARVs for prevention. The timeframe for WHO guidelines is not yet clear.

***Demonstration Projects*:** Demonstration projects are designed to gather information on safety, efficacy and program design for new interventions. They help guide subsequent larger-scale introduction. PrEP demonstration projects are currently ongoing or planned for gay men, other MSM, and transgender women in San Francisco and Miami. There are not yet any demonstration projects planned for women in the US or elsewhere.

***Consensus building*:** A range of PrEP-related consultations have been held to discuss PrEP and its implications. AVAC, UNAIDS and WHO, the Forum for Collaborative Research and many other groups worldwide have helped convene these meetings. Learn more about the debate and agenda at *www.avac.org/prep*.

What is in the PrEP pipeline?

The first generation of PrEP trials focused on tenofovir-based drugs because they are well tolerated, and because there is significant data on their long-term safety and resistance profiles in HIV-positive people. Next generation trials will focus on longer-acting drugs—e.g., those that could be used in injectable form—drugs and drugs that are not widely used for HIV treatment. These include TMC278LA formulated as an injectable and vaginal dapivirine and maraviroc formulated as a vaginal ring).