TDF2 STUDY OF PRE-EXPOSURE PROPHYLAXIS (PrEP) AMONG HETEROSEXUAL MEN AND WOMEN IN BOTSWANA: KEY FACTS

Overview

- Daily oral PrEP with a tablet containing tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, known by the brand name Truvada®) was found to reduce the risk of acquiring HIV infection by roughly 62 percent in the study population overall.
- The level of protection in the trial was strongly related to adherence to the daily regimen:
    - An analysis limited to HIV infections that occurred within 30 days after a participant's last reported drug dose indicated that TDF/FTC reduced the risk of HIV infection by 78 percent.
    - Additionally, blood level data show that participants who became infected with HIV had far less drug in their blood than matched participants who remained uninfected.

Trial Design and Study Population

- Overview: The TDF2 study examined use of a once-daily antiretroviral pill containing tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, brand name Truvada®) as PrEP for HIV infection among young adult heterosexual men and women in Botswana at two sites in Gaborone and Francistown. The CDC study was conducted in partnership with the Botswana Ministry of Health. Additional funding was provided by the National Institutes of Health, and the study drug was donated by Gilead Sciences.

  CDC researchers had anticipated that results from the TDF2 study would only include safety and adherence findings. However, because PrEP was highly effective in this population, the study was able to draw conclusions about overall efficacy (even with a relatively small number of infections occurring in the study population).

- Study Population: A total of 1,219 HIV-uninfected, sexually active, healthy male and female volunteers between the ages of 18-39 in Botswana were enrolled in the trial and randomly assigned to take a daily TDF/FTC pill or a placebo pill. 611 were assigned to take a daily TDF/FTC pill, and 608 were assigned to receive a placebo (overall in the study, 54.3 percent were male, 45.7 percent female). Neither researchers nor participants knew an individual's group assignment.

  Three participants were determined to be HIV-infected at time of enrollment. Those individuals were excluded from the efficacy analysis, which includes data on the 1,216 participants who were HIV-negative at the time they enrolled in the study.

- Informed Consent: To make sure that participants fully understood all aspects of their participation in the trial, all volunteers were required to pass a comprehension test prior to providing written informed consent. Study participants were free to withdraw from the trial at any time and for any reason.

- Prevention Services: To assist participants in eliminating or reducing HIV risk behaviors, extensive risk reduction counseling was provided at each study visit, and more often if needed. Participants were counseled about the importance of adhering to the study regimen and offered free male and female condoms and STD testing and treatment to reduce their risk for HIV infection. The health of participants was closely monitored throughout the trial, and participants were linked to any necessary medical care. All participants who became HIV-infected during the trial were immediately referred to care.

- Scientific and Ethical Review: To ensure that the study remained on a solid scientific and ethical foundation, all procedures and plans were reviewed and approved by scientific and ethical review committees at CDC (called institutional review boards, or IRBs) and the Botswana Ministry of Health (called the Health Research and Development Committee, or HRDC) prior to trial launch. Additionally, trial data were reviewed regularly by an independent data safety and monitoring board (DSMB) to ensure that continuing the trial was safe and scientifically appropriate. CDC worked closely with community partners at each research site to ensure active community participation throughout the course of the trial.

- Retention: While the study experienced challenges with retention in this highly mobile population of young Botswana adults, researchers were ultimately able to secure final data on HIV infection and safety for almost 90 percent of study participants.

Study Results

Efficacy

- In the primary trial analysis of all 1,216 participants who began the trial uninfected, there were nine HIV infections among the 610participants who received TDF/FTC, compared to 24 infections among the 606 assigned to receive placebo. This translates to a 62.2 percent (95% CI, 21.5 to 83.4; p= 0.03) reduction in the risk of HIV infection among those receiving TDF/FTC.
- Among participants known to have a supply of study drugs[i], protection was even greater, with an efficacy of 77.9 percent (95% CI 41.2 to 93.6, p=0.0053). There were 4 infections in the TDF/FTC group and 19 in the placebo group.
- By gender, the CDC TDF2 data suggest efficacy for both men and women. However, because not all of these analyses reached statistical significance, this trial cannot draw conclusions for heterosexual men and women separately. The TDF2 results by gender were:
    - Among all 1,216 participants who began the trial uninfected, the point estimates suggest efficacy for both men and women, but the results were statistically significant only for men:
        - *For men*: There were 2 infections among men receiving TDF/FTC and 10 among those receiving placebo. This translates into a statistically significant HIV risk reduction of 80.1 percent (CI 24.6 to 96.9; p=0.026).

        - *For women*: There were 7 infections among women receiving TDF/FTC, and 14 infections among women receiving a placebo. This translates to an estimated risk reduction of 49.4 percent, but the finding is not statistically significant (95% CI -21.7 to 80.8; p=0.107).
    - Among participants known to have a supply of study drugs[i], point estimates again suggest efficacy for both men and women, but the results reach statistical significance only for women:
        - *For women*: There were 3 infections among women receiving TDF/FTC, and 13 infections among women receiving placebo. This translates into a statistically significant HIV risk reduction of 75.5 percent (CI 23.8 to 94.4; p=0.021).
        - *For men*: Among men receiving TDF/FTC, there was only 1 infection, and 6 infections occurred among men receiving placebo. This translates into an estimated risk reduction of 82.4 percent, but the finding is not statistically significant (CI -2.8 to 99.1; p=0.065).

Adherence & Risk Behavior

- There were no significant differences in overall adherence (based on pill count) or reported sexual risk behavior between the two study arms.
    - Adherence as measured by pill count was high, both among those receiving TDF/FTC and those receiving placebo (84.1 percent and 83.7 percent, respectively).
    - Only half of the participants in the TDF/FTC arm who became infected with HIV had any detectable medication in their blood, and even those participants had very low levels of medication present. This suggests that they had not taken PrEP around the time that they became infected. In contrast, over 80 percent of matched participants who remained uninfected had detectable medication in their blood and their average medication level was substantially higher.
    - Reported sexual risk behavior was similar between the two study arms:
        - Roughly 19 percent of participants in both study arms reported more than one sexual partner in the prior month.
        - The percent of reported vaginal sex episodes with condom use was also similar between the two groups (81.4 percent TDF/FTC vs. 79.2 percent placebo).

Safety & Resistance

- Consistent with other PrEP studies, preliminary analyses did not identify any significant safety concerns associated with daily use of TDF/FTC.
- Participants assigned to receive TDF/FTC experienced an increase in minor side effects – nausea, vomiting, and dizziness. These symptoms lessened after the first month.
- While there was no difference between groups in the rate of bone fractures, participants receiving TDF/FTC experienced a small but significant decline in bone mineral density compared with those receiving placebo
- There was no difference in pregnancy rates between the two study arms.

- Consistent with the previous PrEP trial among MSM (iPrEx), there were no cases of drug resistance among participants taking TDF/FTC who became infected after enrollment.
- One case of TDF and FTC drug resistance occurred in a participant who had unrecognized HIV infection at the time of enrollment and several false negative HIV tests in the months following enrollment. This case underscores the need to ensure PrEP is only used among HIV-negative individuals.

Resources

- For more information on efforts to evaluate and plan for PrEP implementation in the United States, visit www.cdc.gov/hiv/prep.
- For a complete list of PrEP trials being conducted, visit http://www.avac.org/ht/d/sp/i/326/pid/326.
- For information on the results of other heterosexual PrEP trials, visit:
    - Partners PrEP: http://www.uwicrc.org
    - FEM-PrEP: http://www.fhi360.org/en/Research/Projects/FEM-PrEP.htm

###

[i] In this analysis, the follow-up period for all participants was 30 days after the date of their last reported drug dose. All participants received a 30-day supply of study medications at each monthly study visit and were asked to return any unused medication from the prior visit at that time. At the visit when the participant's final supply of study drugs was returned, participants were also asked the date on which they took their last study pill. Participants were followed for an additional 30 days from this date to ensure detection of all acute HIV infections that could have occurred while the participant had a supply of study drugs.