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QUESTIONS AND ANSWERS ABOUT THE CDC TDF2 STUDY AND VOICE

1. What is the TDF2 Study?

The TDF2 Study is a Phase IIb study that assessed the safety, adherence and efficacy of an HIV prevention approach called oral pre-exposure prophylaxis (PrEP). PrEP involves the use of antiretroviral (ARV) drugs commonly used in the treatment of HIV by individuals who are not infected with HIV. In TDF2, researchers evaluated daily use of an ARV called Truvada®, the brand name for a tablet combining tenofovir and emtricitabine, in 1,200 HIV-uninfected heterosexual male and female participants aged 18-39. The study was conducted in Botswana. Tenofovir in tablet form is sometimes referred to as TDF and Truvada is referred to as TDF/FTC. The trial, originally known as the Botswana PrEP Study, began in 2005 as a Phase III trial of tenofovir (TDF). In 2007, researchers decided to evaluate Truvada instead of tenofovir. In 2009, the study met its enrollment target of 1,200 participants, but due to lower than expected HIV incidence and suboptimal retention, it was determined that the study could not answer its primary objective of efficacy without doubling the number of enrolled participants. Instead, the investigators opted to focus on the evaluation of safety and adherence measures.

Of the 1,200 participants in the TDF2 Study, 601 were randomly assigned to take Truvada daily, and 599 were assigned to take a placebo tablet. All participants in the study were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. The CDC study was conducted in partnership with the Botswana Ministry of Health. Additional funding was provided by the U.S. National Institutes of Health, and the study drug was donated by Gilead Sciences.

2. What are the results of the TDF2 Study?

During the course of the study, 33 of the 1,200 participants acquired HIV -- nine of the 601 participants who took Truvada became infected, and 24 participants of the 599 who took placebo became infected. This means that there were 62.6 percent fewer HIV infections in the group of participants assigned to take Truvada daily compared to the placebo group. This result meets the definition for statistical significance, meaning it was not likely due to chance. However, the confidence interval – a statistical term that refers to the range within which the true effectiveness may lie – indicates that the level of effectiveness could be anywhere between 21 and 83 percent.

Despite early difficulties retaining participants, the TDF2 researchers ultimately collected data on more than 90 percent of those enrolled. The CDC released the results of the study on July 13 (2011) and is reporting more details about the study's findings at the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Rome on July 20. Some of the study's data are still being analyzed.

3. What were the differences in results between men and women in the study?

More men enrolled in the study than women; 54.7 percent were men while 45.3 percent of the participants were women. While the results suggest that Truvada was effective in both men and women, few conclusions can be drawn from the results concerning the effectiveness of Truvada specifically in women due to the small numbers of women who became infected during follow-up.

4. What about safety?

No significant safety concerns were identified in the study. Participants assigned to receive the study drug were more likely than those assigned to the placebo arm to report nausea, vomiting, and dizziness, however. These same side effects were observed in the iPrEx Study, which involved men who have sex with men. The researchers reported no differences in the incidence of pregnancies across the two groups.

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5. What are the differences and similarities between the CDC TDF2 Study and VOICE?
The CDC TDF2 Study is comparatively small, with 1,200 participants from two sites in Botswana, and the participants consisted of both women and men. Moreover, the CDC Study evaluated only one ARV –Truvada. VOICE – Vaginal and Oral Interventions to Control the Epidemic – involves only women, with 5,029 participants at 15 sites in Uganda, South Africa and Zimbabwe. VOICE is testing the safety and effectiveness of daily use of the ARV tablets tenofovir and Truvada, but VOICE is also testing daily use of a vaginal microbicide containing tenofovir in gel form. VOICE is the first effectiveness study of an ARV microbicide that women use every day, and the only trial evaluating both a tablet and a gel in the same study. This approach is important for determining how each product works compared to its control (placebo gel or placebo tablet) and which approach women may prefer.

6. When did VOICE begin and how long will it last – when will we know the results?
VOICE began in September 2009, completed enrollment of 5,029 women in June 2011 and is on target to complete follow-up in June 2012. By that time, all women will have used their study product for at least one year, some for nearly three years. Women will then be followed for an additional two months. Results are anticipated to be available in early 2013.

7. How do the results of the CDC study affect VOICE?
The independent Data and Safety Monitoring Board (DSMB) for VOICE has begun the process of reviewing available information from the CDC Study, along with data from Partners PrEP, and will advise the VOICE team and study's funder, the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health, on next steps. During the time that information is being evaluated, and until it is determined the best course for VOICE participants, the study will continue as currently designed.

8. Is VOICE still important?
Globally, women account for 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual intercourse is the primary driver of the epidemic. Young women are especially vulnerable. In southern Africa, young women are up to five times more likely to become infected with HIV than young men, and more than a quarter (26 percent) of all new global HIV infections are among women aged 15-24. Women are twice as likely as their male partners to acquire HIV during sex. Although correct and consistent use of male condoms has been shown to prevent HIV, women are not always able to negotiate their use. Women desperately need methods for preventing HIV that they can control themselves. ARV-based prevention, as either a vaginal gel or an oral tablet, is a promising approach. VOICE will provide important information about the safety and effectiveness of tenofovir gel and the ARV tablets tenofovir and Truvada, and about which method women prefer to use. Moreover, the results from VOICE will provide data that will be key to the U.S. Food and Drug Administration's decision whether to approve tenofovir gel as a method for preventing HIV among women.

9. Do you anticipate changes will be made to VOICE?
We cannot say at this time until after NIAID, the VOICE DSMB and the VOICE team itself have carefully reviewed available data from TDF2, as well as the Partners PrEP Study. After this review, modifications to the study will be made as needed.

10. When will you make a decision whether or not to modify VOICE?
An exact timeline cannot be provided. We will evaluate the information as quickly as possible.

11. The CDC study found that Truvada was effective for reducing the risk of HIV in both men *and* women, so why continue the oral arms in VOICE?
The CDC Study enrolled 1,200 participants, both men and women. Because the participants were randomly assigned in roughly equal numbers to either the placebo or Truvada groups, that means there is data from only 272 women taking Truvada. There were seven women who acquired HIV in the Truvada group compared to 14 women in the placebo group, which translates to 49.4 percent fewer infections in women taking Truvada compared to placebo. However, this finding was not statistically significant – it is possible that the result could be due to chance. The TDF2 Study does not provide sufficient information about the effectiveness of Truvada in women, and it was not designed to evaluate tenofovir. VOICE is designed to evaluate the safety and effectiveness of both ARV tablets, as well as the vaginal microbicide tenofovir gel. The DSMB for VOICE will be reviewing the data from the TDF2 study and advising NIAID and the VOICE team on next step. During the time that information is being evaluated, and until it is determined the best course for VOICE participants, the study will continue as currently designed, collecting data on both the oral tablets and the vaginal gel in VOICE.

12. What are all the studies that have been conducted of Truvada for oral PrEP?
The results of a study called iPrEx, published online in the *New England Journal of Medicine* in November 2010, provided the first evidence that oral PrEP can help prevent HIV. iPrEx found Truvada – together with a comprehensive HIV prevention package – was safe and 44 (43.8) percent more effective than a placebo tablet for protecting against HIV in men who have sex with men. In the Partners PrEP Study, researchers from the University of Washington and their collaborators in Uganda and Kenya, evaluated the safety and effectiveness of daily use of two ARVs – tenofovir and Truvada among men and women in a discordant relationship with a partner who is HIV-positive. The study enrolled 4,758 serodiscordant couples. The results, reported July 13 (2011), the same days as the TDF2 Study, provide the strongest evidence yet in favor of oral PrEP; there were 62 percent fewer HIV infections among participants assigned to take the ARV tenofovir daily compared to participants who took a placebo tablet, and 73 percent fewer infections among those who took Truvada. The TDF2 Study involved 1,200 heterosexual men and women in Botswana and found that 62.6 percent fewer HIV infections had occurred in the group of participants assigned to take Truvada than in the placebo group.

In April 2011, researchers from the FEM-PrEP study announced the trial would be stopping earlier than planned because an interim review of the study's progress by its data monitoring committee determined that even if the study were to continue, it would not be able to conclude whether or not Truvada is effective in its population of women. The study was taking place in Kenya, South Africa and Tanzania. The study team is still collecting data. A final report is not expected until late this year or early 2012.

13. Didn't FEM-PrEP stop early because it found Truvada *wasn't* effective?
No. FEM-PrEP announced in April 2011 that it would be stopping early because it could not conclude one way or another whether Truvada can prevent HIV in high-risk women. Even if it were to continue, the information from the study would still not be enough to support a conclusion about its effectiveness either way. A full analysis of all the study information is needed before we can know what factors might have contributed to FEM-PrEP's inability to answer its research questions. Insight gained from the analysis will in turn help inform the conduct of future clinical trials.

14. What is adherence and why is it so important?
In the context of HIV prevention research, adherence refers to a person's willingness or ability to correctly and consistently follow a regimen. Adherence is important because even the most effective product will not provide benefit if it is not used or not used properly. Indeed, both the iPrEx and CAPRISA 004 studies found that the study product was more effective in those who used it regularly. In iPrEx, which involved men who have sex with men, there were nearly 44 percent fewer HIV infections among participants who were assigned to take Truvada every day than among those who were assigned to a placebo tablet. However, in the men who took the drug more than 90 percent of the time (according to pill counts and self-reports) there were nearly 73 percent fewer HIV infections, and in the men whose blood levels suggested that they took the pills regularly, HIV risk was reduced by more than 90 percent. Similarly, CAPRISA 004 found tenofovir gel reduced the risk of HIV by 39 percent among women who used it before and after vaginal sex compared to women who used a placebo gel, but among women who were considered "high adherers," risk was reduced by 54 percent compared to the placebo group.

VOICE and Data Safety and Monitoring Board (DSMB) Reviews

15. What exactly is a DSMB?
A Data and Safety Monitoring Board (DSMB), also called an Independent Data Monitoring Committee (IDMC), is an independent group of clinical research experts, statisticians, ethicists and community representatives that provides additional oversight of a clinical study. A DSMB regularly reviews data while a clinical trial is in progress to ensure that participants are not being adversely affected by the study or study products. If the DSMB has any safety concerns, it may, at any time, recommend that the study modify its procedures or be discontinued. In addition, the DSMB may recommend halting the trial if there is compelling evidence for a product's effectiveness or if it becomes clear that the trial cannot answer whether a product is effective, a concept called futility. Study protocols define the specific "stopping rules" that would be cause for closing the study for efficacy, harm or futility. A DSMB looks at analyses that are not available to the investigators or anyone else. Restricting certain information to the DSMB while the trial is ongoing helps to maintain the integrity of the study– a study team's knowledge of "blinded" data while a trial is ongoing could easily bias the researchers' conduct of the study and their interactions with participants.

16. How many times has the DSMB met for VOICE, and what is involved in the analyses?
Regular reviews of VOICE are conducted by NIAID's Prevention Trials DSMB. Since the study began in September 2009, the DSMB has conducted four periodic reviews – in December 2009, June 2010, December 2010 and May 2011. The first three reviews focused on safety and study conduct. These reviews indicated no concerns, and the DSMB recommended that the study continue as planned each time. The DSMB review on 9 May, 2011, was the fourth routine review for safety and study conduct and the study's first interim review of efficacy data – an assessment of the number of HIV infections that have occurred in each of the different study groups since the study began. As is the case with any review, the DSMB can recommend continuation of the study without changes or with alterations to the study design, or modification or early termination of the study if there is clear evidence of benefit, harm or that the trial cannot answer whether a product is effective.

17. What was the outcome of the most recent DSMB review of VOICE?
The most recent DSMB review of VOICE occurred on 9 May, 2011. The DSMB recommended that VOICE continue, without changes, to evaluate the safety and effectiveness of daily use of the antiretroviral tablets Truvada or tenofovir, and the vaginal microbicide tenofovir gel for preventing HIV in women.

18. When is the next DSMB review of VOICE?
The next scheduled DSMB review of VOICE is to take place in November 2011. This will be the fifth routine review and the second interim efficacy analysis. In addition to safety and efficacy data, the DSMB will also assess key components of study conduct.

19. What would the DSMB need to see that would cause it to recommend stopping VOICE?
Study protocols define the specific "stopping rules" that would need to be fulfilled in order for the study to be stopped for reasons of efficacy, harm or futility. A DSMB uses these stopping rules as a guide when it reviews a study's interim data. If a threshold has been met as defined in the stopping rules, or if there is very compelling evidence, such as from another trial, the DSMB would likely recommend the study to stop. To stop early for efficacy, there would have to be exceptionally strong indication of a product's benefit, calculated according to a stringent statistical formula applied at different time points in the study. Stopping the study for harm would be warranted if side effects are frequent or serious in nature or if there is indication that use of a product is causing vaginal irritation or inflammation that could make women more susceptible to HIV infection. The study could stop for futility if an intervention shows no evidence of an effect on reducing HIV infection; if the study is having difficulty enrolling women or keeping them in the study; or if it is evident that a large number of women are not using the study product. Any of these situations could compromise the study's ability to answer the questions it was designed to address.

20. Are there plans for the DSMB to talk about these new results with the CDC TDF2 Study?
Outcome of studies can affect other studies. As such, DSMBs will often consider data from other studies in their own reviews. The DSMB for VOICE has already begun the process for a special review of the data from the TDF2 Study, as well as Partners PrEP, and may recommend modifications to VOICE study procedures or design based on that review.

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More detailed information about the CDC TDF2 Study is available at http://www.cdc.gov/hiv/prep/index.htm. Additional information about VOICE can be found at http://www.mtnstopshiv.org/news/studies/mtn003 .

About the Microbicide Trials Network

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners who are devoted to preventing or reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.

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