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QUESTIONS AND ANSWERS ABOUT PARTNERS PrEP AND VOICE

1. What is the Partners PrEP study?

The Partners PrEP Study is a double-blind, placebo-controlled, phase III clinical trial to assess the safety 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. The study enrolled 4,758 discordant couples in Uganda and Kenya in whom one partner was HIV infected and the other was HIV negative. Of these couples, 62 percent involved a male partner who was HIV negative and 38 percent involved a female partner who was HIV negative.

Researchers evaluated daily use of two ARVs: tenofovir and Truvada®, the brand name for a tablet combining tenofovir and emtricitabine. (Tenofovir in tablet form is sometimes referred to as TDF and Truvada is referred to as TDF/FTC.) The couples were randomly assigned to three groups which determined whether the HIV uninfected partner would use tenofovir, Truvada or a placebo tablet during the study. All participants received a comprehensive package of HIV prevention services, which included intensive safer sex counseling (both individually and as a couple), HIV testing, free condoms, testing and treatment for sexually transmitted infections, and monitoring and care for HIV infection. The study began in July 2008 and enrollment was completed in November 2010. Results of the study, which was led by researchers at the University of Washington and funded by the Bill & Melinda Gates Foundation, had been expected to be available late 2012 or early 2013.

2. Why is the Partners PrEP Study being modified?

The independent Data and Safety Monitoring Review Board (DSMB) for the Partners PrEP Study held an ad hoc meeting on Sunday, July 10 to review interim data from July 2008, when the study started, through May 31, 2011. Based on its review, the DSMB concluded that there was clear demonstration that tenofovir and Truvada were effective for preventing HIV among serodiscordant couples, in whom one partner is HIV infected and the other is not. The DSMB recommended that the study continue but that it be modified with the elimination of the placebo group. Participants in the tenofovir and Truvada groups will continue to be followed. Participants in the placebo group will stop placebo medication and thereafter will be offered active product.

3. How effective were tenofovir and Truvada in the Partners PrEP Study?

Among the 4,758 couples, there were 78 participants who acquired HIV through the period ending May 31, 2011. Of these HIV infections, 18 occurred in the tenofovir group and 13 occurred among participants in the Truvada group; 47 participants in the placebo group acquired HIV. This means that compared to placebo, there were 62 percent fewer HIV infections in couples in whom the uninfected partner took tenofovir, and 73 percent fewer HIV infections in those who took Truvada. Both of these results are statistically significant, meaning they are unlikely due to chance alone. Moreover, the confidence interval for each result – a statistical term that refers to the range within which the true effectiveness may lie– adds to the strength of evidence. For tenofovir, 62 percent falls within a range of 34 to 78 percent. For Truvada, 73 percent falls within a range of 49 and 85 percent. Because these confidence intervals overlap, the study was not able to say whether Truvada or tenofovir works better than the other in preventing HIV infection. The Partners PrEP Study had a very high retention rate, with 95 percent of those who enrolled remaining in the study. Adherence was also very high. According to pill counts, more than 97 percent of the study medication was used.

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4. Was there any difference between men and women?
The findings from the interim review of data indicate no difference in the level of protection afforded to men and women in Partners PrEP.

5. What about safety?
There were no safety concerns with either product. There were also no differences in the incidence of pregnancies across the three groups. The team will complete a full analysis of this information, including on the types of side effects that were experienced by participants in the different groups.

6. What are the differences and similarities between Partners PrEP and VOICE?
In Partners PrEP, the target population was men and women who are in discordant partnerships in which one partner is HIV infected and the other is not, and the study was designed to evaluate the safety and effectiveness of daily use of either tenofovir or Truvada by the uninfected partner for decreasing their risk of getting HIV. Partners PrEP enrolled 4,758 couples in Uganda and Kenya. In the majority of these couples, it was the male partner who was uninfected. VOICE – Vaginal and Oral Interventions to Control the Epidemic – involves only women, with 5,029 participants at sites in Uganda, South Africa and Zimbabwe. As with Partners PrEP, 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.

Partners PrEP is unique in its focus on couples in which both partners know their HIV infection status. As such, both the uninfected partner and the infected partner are likely to be very motivated to use PrEP. Indeed, adherence in Partners PrEP was very high. According to pill counts, more than 97 percent of the study medication was used. In VOICE, participants may or may not have information about their partners' HIV infection status, and may not even be in a steady relationship with a single partner. For example, many of the women enrolled in VOICE are unmarried. VOICE is studying a different population of women in a diversity of settings, and it is possible that the efficacy of tenofovir and Truvada may differ in this group of women. It is critical to understand how well oral PrEP works in a wide variety of women in many settings.

7. 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.

8. How does the fact that Partners is stopping early for efficacy of Truvada and tenofovir affect VOICE?
The DSMB for VOICE will be reviewing the data from Partners PrEP and advising 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.

9. How many women in VOICE are in discordant relationships?
Participants in VOICE may or may not have information about their partners' HIV infection status, and may not even be in a steady relationship with a single partner. For example, many of the women enrolled in VOICE are unmarried. VOICE is studying a different population of women in a diversity of settings.

10. 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.

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

12. 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.

13. Why isn't VOICE modifying the study like Partners PrEP is doing? Is it ethical to continue with a placebo?
This is a complicated issue that requires careful deliberation by a variety of stakeholders and communities. Ultimately, what will be decided will be in the best interests of participants and communities and attendant to international standards for the ethical and scientific conduct of clinical trials research.

14. Partners PrEP found that tenofovir and Truvada were effective for reducing the risk of HIV in both men *and* women, so why continue the oral arms in VOICE?
In Partners PrEP, the target population is men and women who are in discordant relationships, with one partner being HIV infected and the other not. In most of the couples enrolled (62 percent) it was the male who was the uninfected partner. So, although Partners PrEP found tenofovir and Truvada worked well for both men and women, the study provides more information about how these drugs can protect heterosexual men from getting infected than it does about how these drugs can protect women from getting infected from a partner with HIV. VOICE involves only women – 5,029 women from Uganda, South Africa and Zimbabwe. And VOICE is testing not only daily use of an ARV tablet – Truvada or tenofovir, but also a vaginal microbicide containing tenofovir in gel form. VOICE will help determine if each is safe and effective for preventing HIV in women, and which women prefer.

It is also important to point out that Partners PrEP is unique in its focus on couples in which both partners know their HIV infection status. In that setting, the motivation for the uninfected partner to use PrEP is likely very high, and indeed, adherence was very high. According to pill counts, more than 97 percent of the study medication was used. In VOICE, participants may or may not have information about their partners' HIV infection status, and may not even be in a steady relationship with a single partner. For example, many of the women enrolled in VOICE are unmarried. VOICE is studying a different population of women in a diversity of settings, and it is possible that the efficacy of tenofovir and Truvada may differ in this group of women. It is critical to understand how well oral PrEP works in a wide variety of women in many settings.

The DSMB for VOICE will be reviewing the data from Partners PrEP and advising NIAID and the VOICE team on next steps. In the meantime, it is important to continue the study and collect data about these regimens.

15. After iPrEx, this now means two studies have found Truvada is effective. What does this mean for the field?
This is a very exciting time for HIV prevention research. The results of 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. Before the Partners PrEP Study, there was more good news from a trial called HPTN 052, which found that antiretroviral therapy given early to an HIV infected partner reduced the risk of HIV infection by 96 percent in the uninfected sexual partner.

Another PrEP study of Truvada, which involved heterosexual men and women in Africa and was conducted by the U.S. Centers for Disease Control and Prevention (CDC), expects to be reporting results soon. The field remains hopeful that the CDC study and VOICE, with results anticipated early 2013, will continue the positive trend and add to the richness of data about the use of ARVs for preventing HIV in different at-risk populations.

16. Didn't FEM-PrEP stop early because it found Truvada *wasn't* effective?

No. FEM-PrEP announced in May 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.

17. 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.

The Partners PrEP Study had a very high retention rate, with 95 percent of those who enrolled remaining in the study, and adherence was also very high. According to pill counts, more than 97 percent of the study medication was used. Had the retention and adherence rates not been this high, the study's findings may not have been as convincing as they were, with 62 percent fewer HIV infections in couples who used tenofovir compared to placebo and 73 percent fewer HIV infections in couples who used Truvada. Adherence is a critical component to the success of any clinical trial evaluating a particular intervention, because if a high percentage of participants fail to follow the study's regimen, it will be difficult to know the true effectiveness of a product or approach.

18. Why was adherence so high in Partners PrEP?

Partners PrEP is unique in its focus on couples in which both partners know their HIV infection status. These couples understand that if they have unprotected sex (or the condom breaks), they are exposing the uninfected partner to virus and greatly increasing their risk of becoming infected. The couples in Partners PrEP were likely to be more motivated than others to adhere to study regimens and pill taking.

VOICE and Data Safety and Monitoring Board (DSMB) Reviews

19. 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.

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20. 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.

21. 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.

22. 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.

23. 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.

24. Are there plans for the DSMB to talk about these new results with Partners PrEP?
Outcome of studies can affect other studies. As such, DSMBs will often consider data from other studies in their own reviews. As soon as possible, the DSMB for VOICE will be conducting a special review of the data from Partners PrEP and may recommend modifications to VOICE study procedures or design based on that review.

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More detailed information about Partners PrEP is available at http://depts.washington.edu/uwicrc/research/studies/PrEP.html. 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.