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QUESTIONS AND ANSWERS

Data and Safety Monitoring Board (DSMB) Reviews and VOICE

Background

1. What is the aim of the VOICE Study?
VOICE – Vaginal and Oral Interventions to Control the Epidemic – is a major HIV prevention trial testing whether antiretroviral (ARV) medicines commonly used to treat people with HIV are safe and effective for preventing sexual transmission of HIV in women. In VOICE, the safety and effectiveness of two different ARV-based approaches are being tested: daily use of an ARV tablet (tenofovir or Truvada®) – an approached called oral pre-exposure prophylaxis, or PrEP – and daily use of a 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. VOICE completed enrollment of 5,029 women in sub-Saharan Africa in June 2011.

2. Who is conducting the study?
The VOICE Study is being conducted by a team of researchers working in the Microbicide Trials Network (MTN), an HIV/AIDS clinical trials network established and funded in 2006 by the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all components of the U.S. National Institutes of Health (NIH). Leading the study are Zvavahera Mike Chirenje, M.D., University of Zimbabwe, Harare, Zimbabwe; and Jeanne Marrazzo, M.D., M.P.H., University of Washington, Seattle, Washington, U.S. As co-sponsors of the trial, CONRAD of Arlington, Virginia, U.S.; and Gilead Sciences, Inc., of Foster City, California, U.S., are providing the study products for free.

3. Where is VOICE being conducted?
VOICE is being conducted at 15 NIAID-funded clinical research sites in South Africa, Uganda and Zimbabwe.

4. When did the trial begin and how long will it last?
The study began in September 2009 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.

5. Why is VOICE 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.

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6. 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 placebo.

The Partners PrEP Study, which has provided the strongest evidence yet in favor of oral PrEP for HIV prevention, had very high adherence among its participants. However, the study is unique in its focus on couples in which both partners know their HIV infection status, and in that both members of each couple had to consent to be enrolled in order to participate. They likely 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. So, as study participants, discordant couples may be much more motivated to adhere to study regimens and pill taking. 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.

7. How is adherence being measured in VOICE?

VOICE researchers recognize the importance of understanding women's adherence to daily regimens of vaginal gel and oral tablets. Even the most promising prevention approach cannot be effective if it's not used. Adherence is evaluated using different measures in VOICE, including counts of tablets or gel applicators at monthly visits, face-to-face interviews and with Audio-Computer Assisted Self Interviewing (ACASI), which allows participants to answer questions about condom use, product use and sexual behavior with greater privacy. Blood samples taken from participants at different times in the study will help determine how well participants followed the study regimens by measuring the amount of drug present. Analysis of drug levels in a type of blood cell called peripheral blood mononuclear cells (PBMCs) is also gaining favor as a very reliable measure of product use. Soon, VOICE trial sites with laboratory capacity will also be collecting PBMCs for this purpose. In addition, the VOICE team is considering the use of another objective measure of adherence that involves analysis of drug levels in hair. If implemented, small samples of hair would be collected only from participants who provide separate consent.

8. What does VOICE do to protect the safety of participants?

The safety of participants in VOICE is and will continue to be the top priority of the research team. VOICE includes numerous measures to monitor and protect the safety and well being of participants, including interim reviews of data by an independent committee called a Data Safety and Monitoring Board, or DSMB. The study team also works actively to decrease participants' risk of HIV infection by providing free condoms, regular counseling about preventing HIV and other STIs, and STI testing and treatment. As with any study, significant concerns about participant safety in VOICE would prompt the study team to take immediate steps to stop participants from using the study products.

The Role of the Data Safety and Monitoring Board in VOICE

9. What is a DSMB?

A Data and Safety Monitoring Board (DSMB) is an independent group of clinical research experts, statisticians, ethicists and often community representatives that provides additional oversight to 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. DSMBs look at data 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. If in its review a 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 cause the study to close for efficacy, harm or futility.

Regular reviews of VOICE are conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Prevention Trials DSMB, which makes its recommendations to the director of NIAID, Anthony Fauci, M.D., who decides whether to accept the DSMB's recommendations. The DSMB for VOICE is composed of representatives from the U.S. and non-U.S. countries, including Africa, who are independent of the study investigators, pharmaceutical sponsor and funding agency, and have no conflicts of interest in the outcomes of the studies reviewed.

10. How many times has the DSMB met for VOICE, and what is involved in the analyses?
Since the study began in September 2009, the NIAID Prevention Trials 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. 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. These reviews indicated no concerns, and the DSMB recommended each time that the study continue, without changes, to evaluate the safety and effectiveness of daily use of the ARV tablets Truvada or tenofovir, and the vaginal microbicide tenofovir gel for preventing HIV in women.

11. When is the next DSMB review of VOICE?
The next DSMB review of VOICE was originally scheduled to take place in November of this year. However, with the release of results of both the Partners PrEP and TDF2 studies in July 2011, the DSMB decided that it would be wise to conduct the full safety and efficacy review earlier. As such, the next DSMB review is scheduled to take place 16 September. This will be the fifth routine review and the second interim efficacy analysis of VOICE. In addition to safety and efficacy data, the DSMB will also assess key components of study conduct, such as study product adherence and participant retention.

12. Will the results of Partners PrEP and the TDF2 studies be considered by the VOICE DSMB?
The results of both the Partners PrEP and TDF2 studies were announced July 13. Because VOICE is testing the same oral products that were evaluated in these studies, the VOICE DSMB met by phone within days of the results being released to discuss their potential impact on VOICE. After careful consideration, the DSMB decided that no changes to study conduct were recommended at that time. The DSMB also decided that it would be prudent to conduct the next full safety and efficacy review of VOICE sooner than originally planned. Rather than hold this review in November, the DSMB will now be meeting 16 September.

The Partners PrEP Study had reported that an ad hoc review by its DSMB found tenofovir and Truvada highly effective for preventing HIV among serodiscordant couples, in whom one partner is HIV infected and the other is not. 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. Meanwhile, the TDF2 Study, which involved 1,200 heterosexual men and women in Botswana, reported that there were 62.6 percent fewer HIV infections in the group of participants assigned to take Truvada compared to those in the placebo group.

13. Isn't the Partners PrEP Study dropping the oral placebo arm because it found that tenofovir and Truvada were effective? Will the VOICE DSMB consider doing the same?
The DSMB review of the Partner PrEP Study revealed that in that study's particular population – men and women in committed relationships with an HIV-infected partner – tenofovir and Truvada were both very effective in reducing the risk of HIV of the uninfected partner. As such, the DSMB recommended that participants in the tenofovir and Truvada groups continue to be followed, but that participants in the placebo group stop placebo medication and be offered active product. Very soon after this announcement, the DSMB for VOICE met by phone to discuss the results of both the Partners PrEP and the TDF2 studies and their potential impact on VOICE. The VOICE DSMB decided that no changes to study conduct were recommended at that time. However, as is the case with any review, the DSMB for VOICE could at any time 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.

New information from other trials can sometimes indicate the need for an ongoing trial to continue, because what one study finds in one group of people at risk of HIV does not mean the same would be true in other high-risk groups, or the study's data may not be sufficient to inform decisions about a product's potential regulatory approval and access. As always, the DSMB deliberates with the best interests of participants and communities in mind and in accordance to international standards for the ethical and scientific conduct of clinical trials research.

14. What are the differences and similarities between Partners PrEP and VOICE?
The target population in Partners PrEP 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 involves only women, with 5,029 participants at sites in Uganda, South Africa and Zimbabwe. 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. 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 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.

15. The FEM-PrEP study was stopped after a similar review. Could that happen with VOICE?
Clinical trials are by their nature very challenging. Despite rigorous and careful planning in all aspects of a study's design and implementation, variables may come into play that are not expected or cannot easily be controlled. In the case of the FEM-PrEP study, its Independent Data Monitoring Board (IDMC) determined that even if the study were to continue it would not be able to determine whether or not Truvada was effective for preventing HIV in its study population of women. As is the case with any review, the DSMB for VOICE 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.

16. 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. For VOICE 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.

Overview of Related Studies

17. 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. Couples were randomly assigned to three groups to determine 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. Gilead Sciences of Foster City, U.S., provided the study products.

18. Why is the Partners PrEP Study being modified?

The Partners PrEP Study DSMB 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. 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 are continuing to be followed and participants in the placebo group will stop placebo medication and be offered active product.

19. 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.

20. What does the Partners PrEP Study tell us about women?

Partners PrEP found tenofovir and Truvada worked well for both men and women. Yet, because in most of the couples enrolled (62 percent) it was the male who was the uninfected partner, 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. In addition, the women in Partners PrEP included only those in committed relationships, and each partner was aware of the other's HIV status. As such, the results may not represent single women, women with multiple partners or those who, though married, may not know whether or not her husband has HIV.

21. What is the TDF2 Study?

The TDF2 Study is a Phase IIb study that assessed the safety, adherence and efficacy of daily use of the ARV Truvada in 1,200 HIV-uninfected heterosexual male and female participants aged 18-39. The study was conducted in Botswana and originally known as the Botswana PrEP Study. It 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 study was sponsored by the U.S. Centers for Disease Control and Prevention and 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.

22. 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.

23. What do the results of TDF2 tell us about women?
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.

24. What is the FEM-PrEP Study?
The FEM-PrEP Study is a placebo-controlled Phase III trial that was designed to test the safety and effectiveness of oral Truvada used daily among higher-risk women between the ages of 18 to 35 in Kenya, Tanzania and South Africa. Higher risk women include those who engage in frequent sexual intercourse or have more than one sex partner. The study began in July 2009 and had intended to enroll approximately 3,900 women, with results available in 2013. However, on 7 April, 2011, the Independent Data and Monitoring Committee (IDMC) overseeing the study conducted a routine interim review of the study's data on 1,951 women who had enrolled before 18 February, 2011. On 14 April, following its review of additional information, the IDMC determined that the study would not be able to answer the questions it was intended to answer about the effectiveness of Truvada for preventing HIV in high-risk women. Consequently, the study's sponsor, now known as FHI 360, decided to stop the study earlier than planned and to complete all follow-up and data collection of enrolled women. FEM-PrEP was funded by the U.S. Agency for International Development (USAID). Early support was also provided by the Bill & Melinda Gates Foundation.

25. What is happening with the FEM-PrEP Study?
Follow-up of enrolled participants is expected to be completed in August 2011. The research team will then conduct a full analysis of all available information. Final results are anticipated to be available end of 2011 or early 2012. Until this final report is available, few conclusions can be drawn about the study.

26. What does FEM-PrEP tell us about women?
Results from the interim review of the FEM-PrEP Study are inconclusive – the study stopped 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 it can be known what factors might have contributed to FEM-PrEP's inability to answer its research questions.

27. What is the status of other studies testing the same products as in VOICE?
Another ongoing study is testing the effectiveness of tenofovir taken daily for reducing the risk of HIV among injection drug users in Thailand. Results of this trial are anticipated in 2012.

Results of the iPrEx Study, which involved nearly 2,500 men who have sex with men, were reported in November 2010. iPrEx found daily use of oral Truvada to be safe, and side effects were infrequent and mild. Moreover, there were 44 percent fewer HIV infections among participants assigned to daily use of Truvada compared to the placebo group.

Last year, a trial called CAPRISA 004 found that tenofovir gel applied before and after sex reduced the risk of HIV by 39 percent compared to placebo. Another study called FACTS 001 is testing tenofovir gel used in the same way and expects to enroll 2,200 women in South Africa. VOICE is evaluating *daily* use of tenofovir gel, regardless of when participants have sex.

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More information and materials about the VOICE Study and related topics are available at the VOICE MTN-003 Web site, http://www.mtnstopshiv.org/news/studies/mtn003

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