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QUESTIONS AND ANSWERS

Decision to Modify VOICE:

Outcome of September 16, 2011 Data and Safety Monitoring Board (DSMB) Review of VOICE

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 – an approached called oral pre-exposure prophylaxis, or PrEP – and daily use of a vaginal microbicide containing an ARV in gel form. VOICE is the first effectiveness study of an ARV-based microbicide that women use every day, and the only trial evaluating both an oral tablet and a vaginal 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 prefer.

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, and how many women are involved?
VOICE is being conducted at 15 NIAID-funded clinical research sites in South Africa, Uganda and Zimbabwe and involves 5,029 women: 4,077 in South Africa; 322 in Uganda; and 630 in Zimbabwe.

4. When did the trial begin and how long is it planned to last?
The study began in September 2009 and completed enrollment of 5,029 women in sub-Saharan Africa in June 2011. Follow-up is planned to be completed in June 2012, when 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. As currently planned, results are anticipated to be available in early 2013.

5. What is the design of the VOICE Study?
VOICE is a Phase IIb (proof of concept) trial designed to evaluate both the safety and effectiveness of two approaches for preventing the sexual transmission of HIV: daily use of an ARV tablet (tenofovir or Truvada®) and daily use of an ARV-based gel (tenofovir gel). Tenofovir and Truvada, the brand name for a combination drug that contains both tenofovir and emtricitabine, are ARVs commonly used in the treatment of HIV.

Learning about the safety and effectiveness of each approach requires the kind of trial in which participants are randomly assigned by chance to different study groups, including groups that may use a placebo, which has no active drug. VOICE has five study groups – two gel groups (tenofovir gel and an inactive placebo gel) and three tablet groups (tenofovir, Truvada and an inactive placebo tablet) – and was designed to enroll approximately 5,000 women, about 1,000 in each group. The study is "blinded," so neither participants nor researchers can know who is in which group while the study is ongoing. Women in the two gel groups are provided identical

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applicators pre-filled with either tenofovir gel or placebo gel, although both gels look identical. Each study participant randomized to the tablet regimen takes two tablets once a day, one that looks like tenofovir and one that looks like Truvada. One contains the oral dose of the drug (or placebo) to which the participant is assigned and the second is an inactive placebo tablet. Women use their assigned study product throughout the time they are in the study, which is an average of 24 months. All participants receive ongoing HIV risk reduction counseling, condoms and diagnosis and treatment of sexually transmitted infections (STIs). To determine which approach women are more likely to use consistently, researchers ask participants a series of standard questions about sexual activity, product use, product use adherence, male condom use and product sharing. Participants also answer the same kinds of questions privately with the help of a computer, an approach that is thought to be a better way to collect sensitive information.

6. What is a DSMB and how does it relate to VOICE?

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 blinded data that are not available to the investigators or anyone else, while a clinical trial is in progress. Based on its review of interim data, a DSMB may, at any time, recommend that a trial, or part of a trial, be stopped if there are concerns about safety, 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. Before a trial begins, study teams 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. The DSMB for VOICE has conducted five routine reviews of the study to date. The most recent DSMB review took place on 16 September, 2011. It was the third review of safety data and the second look at efficacy.

7. What was the outcome of the September 16 DSMB review?

On September 16, 2011, the NIAID Prevention Trials DSMB reviewed VOICE study data for the period between 9 September, 2009 and 1 July, 2011. Based on this interim review, the DSMB recommended that VOICE stop evaluating the oral tenofovir tablet, because it will not be possible for the study to show a difference in effect between the tenofovir tablet and the placebo tablet (futility). Because of this, the DSMB recommended that the women randomized to the oral tenofovir tablet group discontinue their use of the study product. The DSMB made clear in its recommendation that it had no concerns about the safety of any of the study products, including the oral tenofovir tablet. It also made clear that VOICE should continue to evaluate the safety and effectiveness of tenofovir gel and the oral Truvada tablet.

8. How will this change the design of VOICE?

VOICE was designed with five study groups: two gel groups (tenofovir gel and an inactive placebo gel) and three oral tablet groups (tenofovir, Truvada and an inactive placebo tablet), with about 1,000 participants in each group. VOICE will continue to evaluate the safety and effectiveness of tenofovir gel and the oral tablet Truvada compared to a matched placebo for each. This means that instead of five study groups, VOICE will have four: tenofovir gel and placebo gel, and the ARV tablet Truvada and a placebo tablet. After women in the oral tenofovir tablet arm are taken off study product, they will be followed for an additional eight weeks, the normal plan for all participants as they exit off the study. Data from these women will be included in the final data analysis of study results.

9. 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 methods – as either a vaginal gel or an oral tablet – are promising approaches. In this regard, VOICE continues to be an important trial for determining whether tenofovir gel and the oral tablet Truvada are safe and effective, and which method women prefer to use. In particular, data from VOICE on the safety and effectiveness of tenofovir gel will be critical to the U.S. Food and Drug Administration's decision whether to approve tenofovir gel as a method for preventing HIV among women.

Information about the oral tenofovir tablet in VOICE will be important for informing our understanding about oral PrEP in women, and will be critical for informing future research. For these and many other reasons, the research team gratefully acknowledges the significant contributions that each and every VOICE participant – all 5,029 – are making in the effort to prevent HIV.

10. What happens next? When and how will this change be implemented at trial sites?
All VOICE participants are being informed about the decision to modify the study. Because the DSMB had no concerns about the safety of oral tenofovir, the process of discontinuing its use among the participants in that study group can proceed in an orderly fashion. Soon, study staff at each site will receive from the MTN's Statistical Data and Management Center a list of participants who had been randomized to the oral tenofovir tablet group. Because the study is blinded, this information has not previously been known to either the study team or the participants. Beginning no later than October 3, the women identified as having been assigned to use the oral tenofovir tablets will discontinue use of the tablets when they come for their monthly scheduled clinic visit. Eight weeks later, they will return for a last set of tests and procedures, including HIV testing and counseling, before exiting the study. During this last study visit, the participants will be provided information about where they can receive HIV testing and counseling, contraception and other medical or support services as needed. Those women in the oral tenofovir group who became HIV-infected and/or pregnant during VOICE, and subsequently enrolled in an MTN ancillary study, may continue to participate in these studies.

Women in the other two oral tablet groups will stop taking the tablet that looks like tenofovir (small light blue tablet) but is actually a placebo with no active drug. They will continue to take the other tablet, which, depending on the group they had been randomly assigned to be in, is either Truvada or a placebo tablet that looks like Truvada.

The women in the two gel groups will continue to take their study product, either tenofovir gel or a placebo gel.

11. Will the women in the tenofovir tablet group still have an opportunity to participate in CHOICE?
CHOICE – Committed to Having Options for Interventions to Control the Epidemic, or MTN-018, is a follow-up open-label study to VOICE, which would move forward if VOICE finds either the tenofovir gel and/or the oral tablet Truvada safe and effective. VOICE trial participants, including those assigned to the ARV tenofovir tablet group, would be invited to join. If they are interested, they will have access to the study product of their choice (gel or tablet, assuming both methods are effective) during the one-year study. They would also be able to participate in two smaller sub-studies of CHOICE that would investigate product safety among pregnant and breastfeeding women. If at least one product is found to be safe and effective in VOICE, CHOICE would help to inform the broader implementation of oral PrEP and/or the topical gel and be important for understanding the overall safety of these approaches in healthy women of reproductive age.

12. Is the oral tenofovir tablet arm being stopped because tenofovir tablets are not safe?
No. VOICE is stopping the part of the study evaluating the oral tenofovir tablet because it will not be possible to demonstrate that tenofovir tablets are effective in preventing HIV in the women in the study. The DSMB made clear that its review of VOICE study data found no concerns about the safety of oral tenofovir tablets. One of the reasons that tenofovir – an ARV commonly used for treating HIV – was considered for evaluation in VOICE and other HIV prevention trials is because it has an excellent safety profile and has been found to be generally well tolerated by HIV-infected people, including women. Moreover, the Partners PrEP Study, which involved 4,758 serodiscordant couples in Kenya and Uganda, in which one partner was HIV-infected and the other was not, found both oral tenofovir and Truvada tablets effective *and* safe. Still, the safety of our participants in VOICE is and will continue to be the study team's top priority. VOICE includes numerous measures to monitor and protect the safety and wellbeing of participants. As with any study, significant concerns about participant safety in VOICE would prompt immediate steps to stop participants from using the study products.

13. Is the oral tenofovir tablet arm being stopped because of poor adherence?
It is important to recognize that we have no information about the reasons for the DSMB recommendation at this time, other than it was not due to safety. The study is ongoing, and all data remains blinded. It won't be possible to make any conclusions about use of the oral tenofovir tablet in VOICE until after the study has been completed and we have done a full analysis of data from all study groups.

14. There has to be something about the data that led the DSMB to this conclusion. Why isn't there more information? When will we have the answers?
DSMBs analyze data 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. This is because a study team's knowledge of "blinded" data while a trial is ongoing could bias the researchers' conduct of the study and their interactions with participants. This is the same reason why the DSMB cannot provide the VOICE team with more information at this time. VOICE is an ongoing study, and it's important that the decision to discontinue the testing of oral tenofovir tablets does not jeopardize the study's ability to answer important questions about the safety and effectiveness of tenofovir gel and oral Truvada tablets. When the trial is completed and the team has all of the data, there will be a better understanding for the reasons behind the DSMB's recommendation.

15. What does the DSMB's recommendation to discontinue oral tenofovir tell us about tenofovir gel?
The DSMB reviews data from all arms. Had there been any reason to stop or modify the tenofovir gel arm, the DSMB would have done so. It only recommended stopping oral tenofovir tablets, and the reason was not due to any concerns about the safety of tenofovir. While tenofovir gel contains the same active ingredient, it is a different formulation (a gel) and used in a different way (applied vaginally).

16. 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 wellbeing of participants, including interim reviews of data by the NIAID Prevention Trials 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 sexually transmitted infections (STI), 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.

17. How many times has the DSMB met for VOICE, and what were the outcomes of these reviews?
Since the study began in September 2009, the NIAID Prevention Trials DSMB has conducted five periodic reviews – in December 2009, June 2010, December 2010, May 2011 and September 2011. The first three reviews focused on safety and study conduct. The DSMB review on 16 September, 2011 was the study's second 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. In addition to safety and efficacy data, the DSMB also assesses key components of study conduct, such as study product adherence and participant retention. All reviews prior to the 16 September review indicated no concerns, and the DSMB recommended each time that the study continue, without changes.

18. Has the VOICE DSMB considered the recent results of Partners PrEP and the TDF2 studies?
Because VOICE was testing the same oral products that were found effective in the Partners PrEP and TDF2 studies, the VOICE DSMB met by phone within days of those studies' results being released (on 13 July, 2011) to discuss their potential impact on VOICE. After careful consideration, the DSMB decided that no changes to study conduct were necessary. The DSMB also decided that it would be prudent to conduct the next full safety and efficacy review of VOICE sooner than originally planned. So, rather than wait to hold this review in November, the DSMB decided to meet on 16 September, at which time it would have available study data from the trial's start in September 2009 through 1 July, 2011. For its earlier routine review, in May 2011, the DSMB reviewed data for the time period ending 11 March, 2011.

19. When is the next DSMB review of VOICE?
The next routine interim review of VOICE by the DSMB will take place according to the original schedule in mid-November of this year. This will be the study's sixth routine review and the third interim efficacy analysis.

20. Could there be additional modifications to VOICE after the November DSMB review?
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 early termination of the study if there is clear evidence of benefit, harm or futility (meaning the trial cannot answer whether a product is effective). VOICE has defined specific "stopping rules" that would need to be fulfilled in order for the study to be modified or stopped for reasons of efficacy, harm or futility. The DSMB uses these stopping rules as a guide when it conducts interim reviews of VOICE data. As such, 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 can recommend further modifications or that the study stop altogether.

21. Are you disappointed about this outcome?
The DSMB acted in accordance with its charge to ensure that the clinical trials it reviews are conducted ethically and with the highest regard for the safety and wellbeing of study participants. While the study team is disappointed in the outcome, it respects the process by which this decision was made. 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. The VOICE team is especially grateful to all the women who have been participating in VOICE, whose commitment to this study has already helped provide insight about oral tenofovir tablets for preventing HIV in women. This information will have significant implications for a field that faces important decisions about the use of oral PrEP and in which particular populations it could have the most benefit. The team remains committed to completing the trial and, moreover, to providing evidence on whether tenofovir gel and oral Truvada tablets are effective in preventing HIV.

22. This is confusing. Partners PrEP found both oral tenofovir and Truvada tablets effective when used as PrEP by HIV-uninfected men and women who had an HIV-infected partner. But the FEM-PrEP study of Truvada in women was stopped for futility, the same reason that VOICE is closing the tenofovir tablet portion of its study. What does all this mean about the use of PrEP in women?
The Partners PrEP Study demonstrated that in that study's particular population – men and women in committed relationships with an HIV-infected partner, in which both partners consented to enroll in the study – oral tenofovir and Truvada tablets used daily were both very effective in reducing the risk of HIV of the uninfected partner. 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 clear conclusion about its effectiveness compared to placebo. A full analysis of all the study information, which is expected to be available at the end of 2011 or early 2012, is needed before it can be known what factors might have contributed to FEM-PrEP's outcome. VOICE is continuing to evaluate Truvada, as well as tenofovir gel. Not until the study is completed will researchers have information about the safety and effectiveness of these approaches as well as data for the women who had been assigned to the group taking the oral tenofovir tablet.

23. What is the status of other studies testing the same products as in VOICE?
Another ongoing study being conducted by the U.S. Centers for Disease Control and Prevention is testing the effectiveness of the ARV tenofovir taken daily for reducing the risk of HIV among 2,400 injection drug users in Thailand. Results of this trial are anticipated in 2012.

iPrEx-OLE, an open-label extension trial of Truvada in men who have sex with men (MSM), is getting underway at trial sites in South America, the U.S. and South Africa. It follows the iPrEx Study, which found daily use of oral Truvada reduced the risk of HIV by 42 percent compared to a placebo among MSM.

In addition to VOICE evaluating the daily use of tenofovir gel, another study called FACTS 001 will soon begin testing tenofovir gel used before and after sex among women in South Africa. FACTS 001 seeks to replicate the results of CAPRISA 004, which found tenofovir gel applied before and after sex reduced the risk of HIV by 39 percent compared to placebo.

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More information about the VOICE Study and related topics are available at, http://www.mtnstopshiv.org/news/studies/mtn003 . A summary of recent trial results of other PrEP studies can be found at http://www.avac.org/ht/d/sp/i/326/pid/326 .

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