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QUESTIONS AND ANSWERS

The VOICE Study: Vaginal and Oral Interventions to Control the Epidemic

The Big Picture

1. What is the aim of the VOICE Study?

The [VOICE](#) Study – Vaginal and Oral Interventions to Control the Epidemic – is a major HIV prevention trial looking at whether some of the same antiretroviral (ARV) medicines commonly used to treat people with HIV are safe and effective for preventing sexual transmission of HIV in women. VOICE is testing the safety and effectiveness of two different ARV-based approaches: daily use of an ARV tablet (tenofovir or Truvada®), an approach known as oral pre-exposure prophylaxis (PrEP); and daily use of a microbicide containing tenofovir in gel form. VOICE is the first effectiveness study of a microbicide that women use every day and the only trial evaluating both a tablet and a gel in the same study, which will help determine how each product works compared to its control (placebo gel or placebo tablet) and which approach women may prefer. VOICE (also known as MTN-003) has enrolled 5,029 HIV-negative women between the ages of 18 and 45 from communities in South Africa, Uganda and Zimbabwe, where a woman's risk for acquiring HIV through sexual intercourse is among the highest.

2. Why is this study important?

VOICE is focused on sexually active women in sub-Saharan Africa, a population representative of the largest and fastest growing sector affected by the worldwide epidemic. Between 70 and 90 percent of all HIV infections in women are acquired through unprotected heterosexual intercourse. Moreover, women are twice as likely as their male partners to acquire HIV during vaginal 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 a method 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 be a key factor in the U.S. Food and Drug Administration's decision whether to approve tenofovir gel as a method for preventing HIV among women.

3. 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, in Harare; and Jeanne Marrazzo, M.D., M.P.H., University of Washington, Seattle, 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 free of charge.

4. Where is VOICE being conducted?

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

5. When did the trial begin and how long will it last?

VOICE began enrolling women in September 2009 and completed enrollment of 5,029 women in June 2011. Follow-up is expected to be completed in June of 2012, at which time 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 early 2013.

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6. What is a microbicide?

[Microbicides](#) are substances designed to prevent or reduce the sexual transmission of HIV or other sexually transmitted infections (STIs) when applied topically inside the vagina or rectum. A microbicide can be formulated in many ways, such as a gel or cream, or as a ring that releases the active ingredient gradually over time. Several microbicide products are being tested in clinical trials, including in trials being conducted by the MTN, although none is currently approved or available for general use.

7. What is pre-exposure prophylaxis (PrEP)?

[Pre-exposure prophylaxis](#), or oral PrEP, is an experimental HIV prevention approach that involves use of ARVs by people who are HIV-negative. The idea is that by taking a medicine routinely – daily, for example – HIV infection would be prevented if a person were exposed to the virus, such as through unprotected sex.

8. What microbicide is being studied in VOICE?

VOICE is evaluating a candidate vaginal microbicide called [tenofovir gel](#), which is among a class of candidate microbicides based on drugs that act specifically against HIV. In its oral tablet form, tenofovir is approved as a treatment for HIV infection in combination with other drugs. Each dose of tenofovir gel contains approximately 40 mg of active drug. Laboratory and animal studies have demonstrated that tenofovir gel acts on certain cells of the vagina and cervix that are the primary targets for HIV infection. Clinical safety studies performed to date have found the gel to be well tolerated and safe. An expanded safety and acceptability trial called [HPTN 059](#) found daily use of the gel over six months by sexually active HIV-negative women was safe and well-tolerated. Reported side effects have been minor and include dryness, itching, burning or discomfort in the genital area. More recently, the [CAPRISA 004](#) study found tenofovir gel was safe and 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. A larger study of the same dosing regimen, called FACTS 001, is expected to start September 2011.

9. How is VOICE different from the CAPRISA 004 and FACTS 001 trials of tenofovir gel?

[CAPRISA 004](#) was a Phase IIb trial conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) that assessed the safety and effectiveness of tenofovir gel among women who applied it within 12 hours prior to sex and as soon as possible within 12 hours after sex. The study was conducted at two sites in the KwaZulu-Natal province of South Africa and involved 889 women. As a follow-up to CAPRISA 004, FACTS 001 is a larger study of the same regimen being spearheaded by a South African-based research consortium. FACTS 001 plans to enroll 2,200 women at seven sites in South Africa. Unlike the CAPRISA 004 and FACTS 001 studies, VOICE is evaluating *daily* use of tenofovir gel, regardless of when participants have sex. Moreover, VOICE is also testing two different oral ARV tablets – tenofovir and Truvada – to help determine how well each product works compared to its control (placebo gel or placebo tablet) and which approach women prefer to use. VOICE has enrolled 5,029 women from multiple regions in South Africa as well as from Uganda and Zimbabwe. Despite these differences, the three studies complement one another, and each is critical to advancing understanding about the safety and effectiveness of tenofovir gel using different strategies among different populations of African women, as well as for providing insight about the particular regimen women in Africa may be more likely to use.

10. Which ARVs are being tested in VOICE?

VOICE is evaluating two ARV tablets, [tenofovir](#) and [Truvada](#). The full name for tenofovir is tenofovir disoproxil fumarate (TDF) and it is known by the brand name Viread®. Truvada is the brand name for a combination drug that contains tenofovir and emtricitabine (FTC) and is sometimes referred to as TDF/FTC. Tenofovir and Truvada are approved for the treatment of HIV when used in combination with other ARVs, a regimen called antiretroviral therapy (ART). Both drugs belong to a class of anti-HIV medications called nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs) that act against HIV by targeting a key enzyme the virus needs to copy its genetic material – an essential step for the virus to multiply and infect other cells inside the body.

Participants in VOICE who are assigned to use either tenofovir or Truvada are given the same daily dose used to treat HIV. Tenofovir is a 300 mg tablet. A single Truvada tablet contains 300 mg of tenofovir and 200 mg of FTC. Both drugs have excellent safety profiles and are well tolerated by most HIV-infected people. In some, minor side effects can include upset stomach, dizziness, headache, rash, joint pain or fever. Serious side effects are rare, but can include liver function problems, kidney damage or failure, or reduction in bone mineral density. Much less is known about the safety and side effects of these drugs in HIV-negative people, but results of oral PrEP studies reported in the last year have indicated no safety concerns. In a minority of participants, side effects such as mild nausea and diarrhea were experienced in the first few weeks of starting study product.

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11. What have other trials of oral PrEP found?

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 – safe and 44 percent more effective than a placebo tablet for protecting against HIV in men who have sex with men. Results of the Partners PrEP Study, reported in July 2011, have provided the strongest evidence yet in favor of oral PrEP. Partners PrEP evaluated the safety and effectiveness of daily use of tenofovir and Truvada among 4,758 serodiscordant couples in Kenya and Uganda, in which one partner was HIV-infected and the other was not. There were 62 percent fewer HIV infections among participants assigned to take tenofovir daily compared to participants who took a placebo tablet, and 73 percent fewer infections among those who took Truvada. Similarly, the TDF2 Study found that in its study of 1,200 heterosexual men and women in Botswana there were 62.6 percent fewer HIV infections in the group of participants assigned to take Truvada than in the placebo group.

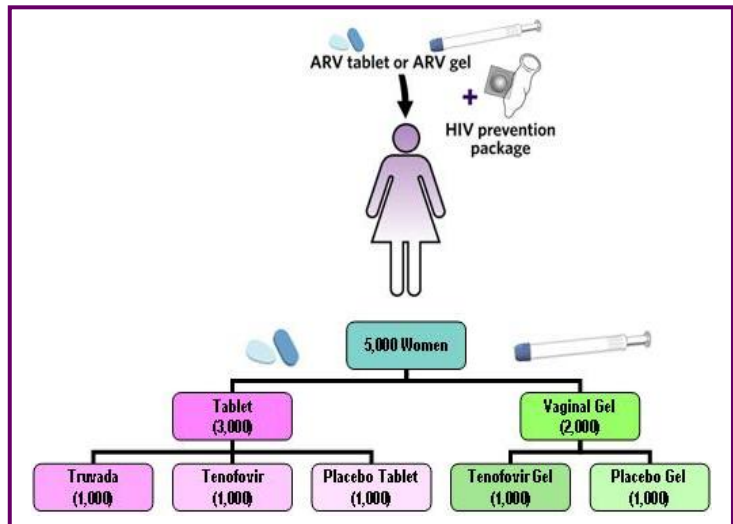
On the other hand, information from a study called FEM-PrEP is inconclusive. In April 2011, researchers announced that the trial would be stopping earlier than planned because an interim review of the study's progress by its data monitoring committee determined that even if the study were to continue, it would not be able to conclude whether or not daily Truvada is effective in the women who had enrolled at sites in Kenya, South Africa and Tanzania. The study team is still collecting data; a final report is expected late 2011 or early 2012.

In addition to VOICE, there is only one other large-scale effectiveness PrEP trial currently ongoing. The other trial 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.

12. How is the VOICE Study designed?

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).

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. 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 know who is in which group. Women in the two gel groups are provided identical 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 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.

13. What is the reason for using the gel every day in VOICE?

VOICE was designed according to current understanding about the mechanisms of tenofovir. As such, researchers conducting VOICE believe that using gel every day will provide cells with a sufficient level of drug needed for continuous protection. For the drug to work against HIV, it must be in its activated form, which requires that it first

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get inside a target cell and then add two protective molecules, called phosphates, to its structure. It takes tenofovir a bit of time to forge this shield, and the protection it offers gradually subsides. Researchers see daily dosing as a way to supply cells with a steady stream of reinforcements, providing a sustained defense against HIV.

14. Why evaluate both a vaginal gel and oral tablets in the same study?

Although HIV infection rates are beginning to decline in some parts of the world, sub-Saharan Africa continues to bear the burden of the epidemic. Because women and girls are especially vulnerable, there is an urgent need for multiple prevention strategies. Two promising strategies involve the use of anti-HIV drugs, as either a vaginal gel or an oral tablet. It is not enough to determine that these strategies are safe and effective for protecting against sexual transmission of HIV. Understanding which approach women are more likely to use is also critical, because no method can ever be effective if women don't use it. A single trial designed to evaluate both approaches can provide the greatest insight and the most scientifically reliable information about the effectiveness, safety and women's preferences for each.

15. Why is VOICE testing two drugs for oral PrEP but only one vaginal gel?

MTN researchers consulted many experts, including a group convened by NIAID's Division of AIDS, to help determine whether the VOICE Study should evaluate as oral PrEP tenofovir only, Truvada only or both drugs. Consensus weighed heavily in favor of studying both drugs, because this would allow researchers a unique opportunity to better assess their safety and effectiveness in an important at-risk population. The same decision was reached by University of Washington researchers when they designed the Partners PrEP Study, which involves men and women in a discordant relationship with a partner who is HIV-positive. VOICE is testing tenofovir gel; a gel formulation of Truvada is in early stages of development but is not yet ready for testing in humans.

16. How are the women in VOICE different than the women enrolled in the Partners PrEP Study?

VOICE involves 5,029 women from Uganda, South Africa and Zimbabwe who may be married or single or have more than one partner or no partner at any given time. Even those women in a committed relationship may not have information about their partners' HIV infection status. Partners PrEP enrolled both men and women who were in discordant relationships, with one partner being HIV infected and the other not and both partners knowing each other's HIV status. Importantly, *both* members of the couple—the man and the woman—had to consent to enroll to participate in the Partners PrEP Study.

17. Who manufactures the study products being tested in VOICE?

Gilead Sciences, Inc., of Foster City, California, U.S., developed all three study products. While it continues to market tenofovir and Truvada, Gilead assigned a royalty-free license for the vaginal gel to CONRAD, of Arlington, Virginia, and the International Partnership for Microbicides of Silver Spring, Maryland, in 2006.

18. What if VOICE finds the products to be effective?

MTN is planning a follow-up study to VOICE, which would move forward if VOICE finds either or both the gel and the tablets (tenofovir and Truvada) safe and effective. CHOICE – Committed to Having Options for Interventions to Control the Epidemic, or MTN-018, is designed as an “open-label” study that former VOICE trial participants would be invited to join, and if interested, have access to the study product of their choosing (gel or tablet, assuming both methods are effective) during the one-year study. CHOICE will also include about 300 women who did not take part in VOICE or any other HIV prevention study. CHOICE would represent a critical step toward making tenofovir gel and/or the tablets more widely available to women at risk of HIV. CHOICE will allow researchers to collect additional safety data that would be required for licensure of the study products – in particular, tenofovir gel – for preventing HIV in women. CHOICE will also help to understand women's preferences for the gel and tablets and what level of safety monitoring is most practical and conducive to women's adherence to either regimen – matters to consider in the “real world. As such, CHOICE would help to inform the broader implementation of oral PrEP and/or the topical gel. Two smaller sub-studies of CHOICE would investigate product safety among pregnant and breastfeeding women, which will be important for understanding overall safety in healthy women of reproductive age.

19. Will tenofovir gel or the ARVs being tested in VOICE ever be made more broadly to women for use as HIV prevention?

In October 2010, the FDA indicated that it would decide whether to approve tenofovir gel as an HIV prevention method for women primarily on the basis of two pivotal trials: CAPRISA 004 and VOICE, which is expected to report results in early 2013. The FDA also granted the gel Fast Track designation, which allows for its expedited

review of all data submitted in support of drug licensure, including the additional safety data that CHOICE would provide as well as results from other tenofovir gel studies. Because drug regulatory authorities in other countries are often guided by what the FDA decides, U.S. approval would help to facilitate availability of the gel in parts of the world where it is most needed.

FDA approval would also make it more likely that the gel could be distributed through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) program. FDA approval of a drug does not guarantee its access in all countries, however. Some regulatory authorities may require different kinds of studies or data. For instance, while the FDA does not require the results of FACTS 001 in its review, the Medicines Control Council in South Africa or another in-country regulatory agency might. As co-licensees for tenofovir gel, CONRAD and the International Partnership for Microbicides are leading all discussions with drug regulatory authorities and working to ensure that individual requirements are met. In the meantime, CONRAD has granted the South African Government's Technology Innovation Agency (TIA) rights to manufacture and distribute tenofovir gel in Africa. The gel, if approved, would be registered, manufactured and distributed by ProPreven, a joint venture involving TIA, Cipla Medpro and iThemba Pharmaceuticals.

While a number of trials have provided strong evidence showing that daily use of an ARV tablet such as tenofovir or Truvada can reduce HIV in some high-risk populations, stakeholders and ultimately the governments and health ministries of each country will need to consider what level of evidence is acceptable and for which populations before deciding if and how to make oral PrEP available as HIV prevention. Before implementing ARV-based prevention programs, clinical guidelines and standards will need to be in place, especially where tenofovir and Truvada and similar ARVs are used as first-line HIV treatment. For instance, there would need to be a provision for HIV screening, along with ongoing HIV testing, to prevent the inadvertent use of ARVs by people who are already HIV-infected. Finally, governments and health ministries will need to determine how available resources can be optimized for integrating treatment and prevention services that best address the individual needs of different communities.

At the Trial Site

20. What kind of approvals were needed before this study could get underway?

VOICE underwent extensive and rigorous review by NIAID and the U.S. Food and Drug Administration (FDA). Moreover, before any site could begin enrolling women into the study, approvals were required of government and regulatory authorities in the trial site country and the site's Institutional Review Board (IRB) or Ethics Committee (EC). IRBs and ECs ensure that studies are scientifically valid and ethically sound and provide oversight throughout the duration of the trial.

21. Do women participating in the study provide informed consent?

Women who volunteer to join the study are told about all the study procedures, any possible risks, benefits and alternatives to participation as well as the study's time requirements. Study staff also explain that women do not have to join and can leave the study at any time, without consequence. This process is called "Informed Consent" and it occurred prior to screening for the study, again at enrollment, and continues throughout the duration of the study. Information is provided in simple terms and translated into local languages. Site community educators and Community Advisory Board (CAB) members also play important roles in helping prospective participants understand the study.

22. What is being done to ensure the safety of participants in VOICE?

VOICE was designed based on rigorous international medical practice and ethical standards and includes numerous measures to protect the well-being of participants. Potential volunteers were carefully screened by study staff to ensure that only women for whom it would be medically safe to participate were enrolled. Although the ARVs being used in VOICE are usually safe and cause few side effects when used as part of treatment in HIV-infected people, there is much less information about their use in people who are HIV-negative. As such, VOICE involves clinical teams at the trial sites who perform thorough checks on the health, safety and welfare of participants at each study visit; a team at the MTN statistical and data management center (SDMC) that assesses incoming reports on a daily basis; and a VOICE protocol safety review team (PSRT) that provides regular monthly oversight. The PSRT includes three additional MTN physicians – two specializing in infectious diseases and HIV and the other in obstetrics and gynecology – whose sole responsibilities are to ensure that everything possible is being done to monitor and protect the safety of participants.

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Regular reviews are also conducted by an independent Prevention Trials Data and Safety Monitoring Board (DSMB) that oversees clinical trials funded by NIAID 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.

23. What happens if a participant becomes HIV-positive while enrolled in VOICE?

All women in VOICE receive a comprehensive HIV prevention counseling and services throughout the trial that include free condoms, risk-reduction counseling, regular HIV testing and other provisions. Despite these intensive efforts, a participant could become infected if she has unprotected sex with a partner who has HIV. Women in the trial who test positive for HIV are taken off study product immediately because continuing its use could increase the risk of the virus becoming resistant to that drug; and they are counseled and referred by study staff to local HIV care and support services. Providers and programs to which participants are referred offer psychosocial services and medical care, including antiretroviral therapy. Women are encouraged to remain in the VOICE Study and continue with routine study visits. When possible, they also are referred to other local research studies for HIV-infected women. In addition, VOICE Study participants who become infected are invited to participate in another MTN study called [MTN-015](#). Although MTN-015 does not provide HIV treatment, with a participant's permission, researchers can maintain close contact with her primary treatment provider and share results of laboratory tests that are performed as part of the study, which may suggest modifications to her treatment and help improve the level of care.

24. How could a woman become HIV-positive while taking part in a trial of a microbicide or oral PrEP, approaches meant to prevent HIV?

In sub-Saharan Africa, where the VOICE Study is being conducted, a woman's risk for acquiring HIV through sexual intercourse is greater than in any other part of the world. To reduce the risk of HIV for women participating in its trials, MTN researchers provide trial participants free condoms, frequent HIV testing and HIV risk-reduction counseling, including on the use of condoms, and routine testing and treatment for STIs. Despite these intensive, ongoing efforts, a woman who participates in a trial like VOICE could acquire HIV if she has unprotected sex with a partner who is infected with the virus.

25. Is there concern that women who become HIV-infected will develop drug resistance to either tenofovir or Truvada?

It's important to understand that [drug resistance](#) is only possible in someone infected with HIV, and the study's primary interest is reducing the risk of HIV infection in all women who participate. If a woman becomes infected despite the study's efforts, safeguards are in place to minimize the potential for drug resistance. For instance, women in VOICE are tested for HIV at every monthly visit. If a test indicates that a woman has acquired HIV, staff will immediately stop her use of study product, because its continued use can increase the chance that virus will become resistant to the drug. Women testing positive for HIV in VOICE will be monitored for resistance so that if identified, it can be managed appropriately by those treating the infection. Resistance to one ARV does not reduce the effectiveness of all ARVs. Most types of drug resistance can be readily managed by stopping the ineffective ARV drug and starting a new combination of drugs. Still, researchers don't know if or to what extent drug resistance might occur in women who become infected while enrolled in the study. VOICE and similar studies will provide important information.

26. What is the VOICE Study doing to reduce the risk of drug resistance?

VOICE includes several safeguards to minimize the potential for [drug resistance](#). Researchers screened all prospective participants for HIV infection to avoid enrolling anyone who is already HIV-infected, and women who have been enrolled in the study undergo monthly HIV testing so that investigators can quickly identify women who may have acquired HIV and immediately stop their use of the study drug (tablet or gel). In addition, study products are dispensed monthly – and only after results of HIV testing are known to be negative – to prevent an infected participant from continuing to use the study product. This is especially important as neither the researchers nor the participants know if the study product they were randomly assigned to use contains an active drug or a placebo. Based on current understanding about viral resistance, VOICE researchers believe that these and other procedures will help minimize the potential that a drug-resistant virus will develop or persist in women who acquire HIV while in the study.

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27. How will you know if a woman has drug resistance?

Women who become HIV-positive while enrolled in VOICE will be tested often for the presence of HIV [drug resistant](#) virus using both standard and highly sensitive methods. Women who chose to participate in [MTN-015](#) will have additional tests for resistance performed so that researchers can determine its prevalence and patterns over time. Tests that are performed as part of MTN-015 may suggest modifications to her treatment and help improve the level of her care.

28. Does VOICE provide antiretroviral therapy, or ART, to women who acquire HIV?

MTN receives funding to conduct clinical trials only, and is not permitted to provide HIV treatment. However, all MTN trial sites must have agreements with local providers so that if a study participant acquires HIV she can be referred to the appropriate services and care in her community. In addition, site staff offer women the opportunity to participate in another MTN study, [MTN-015](#). As a long-term observational study, MTN-015 does not provide HIV treatment, but frequent laboratory tests indicating how the disease is progressing and how women are responding to treatment can help local treatment providers better manage the clinical care of these women.

29. The VOICE Study includes a lot of monitoring of bone health. What does that have to do with HIV prevention?

Researchers have observed that HIV-infected women who are treated with an ART regimen that includes tenofovir can experience modest decreases in bone mineral density (thinning of bone). If tenofovir and Truvada are to be considered approaches for preventing HIV it will be important to understand the effects, if any, on bone in women who are otherwise in good health. It is especially important to gain understanding of the potential effects on women in sub-Saharan Africa, who are among those at highest risk for acquiring HIV. As such, all participants in the VOICE Study undergo regular monitoring to assess how product use may be affecting bone. In addition, a separate, more focused study on bone health, called [VOICE B](#), is being conducted at VOICE sites in Uganda and Zimbabwe in a subset of VOICE participants who have been randomly assigned to the oral tablet regimen.

30. Are you concerned that participants in the study will feel a false sense of protection and be more apt to engage in high-risk behaviors?

Participants are counseled at each visit about the importance of adhering to the study regimens and safe sex practices. They are also reminded that none of the products being tested has been proven effective in preventing HIV, and that not all women participating in the study may be using an active product.

31. ARVs are in short supply for HIV-infected individuals, so aren't you concerned participants will share or sell study products?

Study products are dispensed only to enrolled participants upon receipt of a written prescription from an authorized prescriber, and each prescription is usually limited to a one-month supply of tablets or gel. Participants are counseled monthly about the importance of adhering to study regimens and the dangers posed by sharing study products with other participants or others not in the study, especially since not all women will be assigned to an active product.

32. 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, which has provided the strongest evidence yet in favor of oral PrEP for prevention, also reported very high adherence among its participants. However, the study involved serodiscordant couples, in which both partners know their HIV infection status; these couples may be much more motivated to use PrEP than

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participants in other trials. Still, 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 how effective a product or approach really is.

33. 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, because not even the most effective prevention approach will 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, 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.

34. What kind of barriers might prevent women from fully complying with study regimens?

As a sub-study of VOICE, [VOICE C](#), also called the Community and Adherence Sub-study, aims to identify specific factors within a participant's household, her social environs or the broader community that can influence her willingness or ability to correctly and consistently follow either regimen. VOICE C will include a subset of women enrolled in VOICE, but also their male partners, members of a clinical research site Community Advisory Board (CAB) and key community stakeholders. In total, about 275 participants will take part. VOICE C will provide important insight about the specific factors that can determine whether a woman is willing and able to commit to using a vaginal gel or tablets to reduce her risk of HIV, information that will be essential for the design and implementation of new HIV prevention trials and the eventual rollout of products found to be effective and approved for use.

35. What happens to women who are breastfeeding or who become pregnant?

Pregnant women and women who were breastfeeding at the time of screening could not join the VOICE Study because researchers are still studying the effects of tenofovir, Truvada or tenofovir gel on a woman's pregnancy or the development of her fetus, or on her baby if she uses the gel or tablets while breastfeeding. Women who have been enrolled must not be planning to become pregnant during the study and must use effective contraception and have monthly pregnancy tests throughout the trial. If a participant becomes pregnant during the study, she must stop using the study products, but will remain in the study and continue with all trial site visits. She will also be referred by study staff to available sources of medical care and other services that she or her baby may need. Depending on the timing of pregnancy relative to the study's progress, some women may be able to resume using gel or tablets, provided they are no longer breastfeeding. Women who become pregnant will also be invited to participate in MTN's [Prevention Agent Pregnancy Exposure Registry](#), also known as [EMBRACE](#) (Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure), which is a first-of-its-kind observational study of women who become pregnant during an HIV prevention trial and pregnant women who participated in separate MTN safety studies.

36. What are the medical benefits for women participating in the study?

Study participants receive free laboratory tests and physical exams, HIV prevention counseling and free condoms. STI risk-reduction counseling, testing and treatment are provided at no charge to both women and their partners. In addition, VOICE provides effective contraception and monthly pregnancy and HIV testing. Participants who acquire HIV during the trial are counseled appropriately and receive referrals to community-based programs for care and support. They are taken off study product, but have the option to remain in the trial and receive all scheduled safety evaluations.

37. If women participating in this study use condoms, how will you know if the gel or ARV is effective for preventing HIV?

In order to reduce the risk of HIV for all women in the trial, researchers provide participants free condoms and HIV risk-reduction counseling, including on the use of condoms, and routine testing and treatment for STIs. If every

single participant used a condom for every act of sexual intercourse during the course of the study, it would be nearly impossible for researchers to evaluate the effectiveness of microbicides or oral PrEP. Unfortunately, as is true in the “real world,” women are not always able to convince their partners to use condoms or to use them all the time. Once the study is completed, results are analyzed taking into account the number of times women reported using condoms during each sex act.

38. Why is VOICE only being conducted in Africa?

The MTN has clinical trial sites in Africa, India and the United States, but not all of these sites are in places where the rates of new HIV infections are as high as they are in Africa. In places where the risk for HIV infection is high, researchers can determine more quickly and with greater certainty whether a certain product is working. More importantly, women in sub-Saharan Africa represent the largest and fastest growing at-risk population for HIV, and they have the most to gain if this trial or any other trial identifies a safe and effective method for preventing HIV.

39. How does the VOICE Study involve the community?

The MTN is guided by an agenda that seeks to foster participation by and collaboration with representatives of diverse scientific disciplines related to HIV prevention, as well as from the lay communities in which MTN trials are being conducted. MTN’s trial site Community Advisory Boards (CABs) play an essential role, as do community and advocacy groups, in many stages of protocol development and study implementation. MTN’s Community Working Group (CWG), comprised of community educators and CAB members from each clinical research site, is particularly engaged, and for VOICE, has provided input on the protocol, community education strategies, informed consent process and many of the study’s procedures. Before VOICE began, the MTN also sought consultation with leading African advocates working in HIV prevention, treatment access and women’s health. MTN leadership acknowledges that an understanding of the purpose, methods and limitations of clinical research is vital for meaningful community input into study design and implementation, and that true community participation in HIV prevention research requires a level of ownership throughout the research process. As such, all trials sites have active community engagement programs with local non-governmental organizations, activist groups, journalists, local physicians, health department officials and other stakeholders. These activities involve locally designed approaches and methods to make the science clearly accessible to lay people, including those with little or no formal education.

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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), <http://www.mtnstopshiv.org/news/studies/mtn003>.

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