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QUESTIONS AND ANSWERS

MTN-001
Adherence and Drug Absorption Study of Oral and Vaginal Gel Formulations of Tenofovir

1. What was the aim of MTN-001?
MTN-001 was a Phase II trial conducted between 2008 and 2010 that compared the oral tablet and vaginal gel formulations of the antiretroviral (ARV) drug tenofovir, looking at differences in how the drug is absorbed in vaginal tissue and blood and women's preferences or ability to adhere to daily regimens of each approach separately and in combination. While ARVs like tenofovir are commonly used in the treatment of HIV, ARV-based approaches, such as those studied in MTN-001, have also been tested for preventing HIV. As such, MTN-001 was designed to address specific questions about daily use of tenofovir gel and the oral tablet in HIV-negative women and to help in better understanding the results of large-scale HIV prevention trials, particularly VOICE. VOICE – Vaginal and Oral Interventions to Control the Epidemic – tested the safety and effectiveness of oral tenofovir; Truvada®, an oral tablet that contains both tenofovir and emtricitabine; and tenofovir gel, among 5,029 women in Africa.

2. Who conducted and funded the study?
MTN-001 was funded by the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID) and conducted by a team of researchers working in the Microbicide Trials Network (MTN). Craig W. Hendrix, M.D., of Johns Hopkins University, led the study. The MTN is an HIV/AIDS clinical trials network established and funded in 2006 by DAIDS/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). As co-sponsors of MTN-001, CONRAD of Arlington, Va., and Gilead Sciences, Inc., of Foster City, Calif., provided the study products free of charge.

3. Who participated in MTN-001 and where was it conducted?
MTN-001 enrolled 144 healthy, HIV-uninfected women evenly divided between four sites in the U.S. and three in Uganda and South Africa. The U.S. sites were Case Western Reserve University in Cleveland; University of Pittsburgh; University of Alabama at Birmingham; and Bronx-Lebanon Hospital, Columbia University, in New York. In Uganda, MTN-001 was conducted at Makerere University-Johns Hopkins University Research Collaboration in Kampala; and in South Africa, at the Umkomaas and Botha's Hill clinical research sites affiliated with the Medical Research Council of South Africa in Durban.

4. What are the results of MTN-001?
The final results of MTN-001's pharmacokinetics (drug absorption and distribution) studies, which were published Jan. 30, 2013 in the online journal *PLOS ONE,* found that daily use of the vaginal gel achieved a more than 130-times higher concentration of active drug in vaginal tissue than did the oral tenofovir tablet. Compared to tenofovir gel, the tablet was associated with a 56-times higher concentration of active drug in blood. All three daily regimens (vaginal gel, oral tablet and the two combined) were well tolerated by the women in the study. Nausea occurred in 15 percent of the women when using the tablet and 14 percent when using the gel and tablet together. Vaginal itching and irritation were the most common side effects with the gel.

According to the study's results on adherence and acceptability reported in *AIDS and Behavior* in October 2012, self-reported adherence was very high (94 percent), with many participants saying they liked both products. Drug serum concentrations, however, indicated that only 64 percent of the women, at best, took the tablets consistently. Interestingly, the women enrolled at the U.S. sites were more adherent to pill taking than the women enrolled in Africa. As for which approach they preferred, 72 percent of the U.S. women said they liked taking the tablet, compared to 14 percent who preferred using the gel. The African women liked both products: 42 percent favored the gel, 40 percent preferred the tablet and 14 percent liked them both equally.

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5. Why is MTN-001 important?
MTN-001 was the first study in which head-to-head comparisons were made between tenofovir gel and oral tenofovir – and in every study participant. As such, it has provided important information about how the active drug is taken up in vaginal tissue and blood with each formulation and insight about women's preferences for and their ability to adhere to each regimen. The results of MTN-001 are especially important in the context of outcomes of HIV prevention trials testing the same approaches and/or products in different high-risk populations, including women in sub-Saharan Africa. MTN-001's findings suggest that tenofovir gel should be highly effective and that it should be significantly more effective than oral tenofovir when used by women to prevent HIV infection. Yet, tenofovir gel was only moderately effective in the CAPRISA-004 study (when used before and after sex) and not at all effective in VOICE (in which women were asked to use the gel daily). In contrast, several trials of daily use of tenofovir alone or of Truvada (a tablet that contains tenofovir) showed levels of effectiveness that were much higher than MTN-001 data would have predicted. MTN-001researchers have, therefore, concluded that other factors besides tissue drug concentration can affect whether or not a product is effective in different groups of people. These may include adherence to product use, a particular feature of the gel formulation or a biological reaction that may be associated with vaginal gel delivery of tenofovir, among others. The results of VOICE, which are expected to be reported at the Conference on Retroviruses and Opportunistic Infections (CROI) in early March (2013), may help to understand if the reasons that tenofovir gel and oral tenofovir were not effective were due to these or other factors, as well as determine whether Truvada was safe and effective for protecting against HIV in women.

There is an urgent need for effective and easy-to-use prevention strategies that women can control themselves. Women account for 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual intercourse is primarily to blame for the region's heavy HIV burden. Young women are especially vulnerable. Efforts to promote abstinence, monogamy and male condom use haven't been enough to stop the HIV epidemic nor are these methods feasible in most settings.

6. What is known about the products that were studied in MTN-001?
MTN-001 studied the tablet and topical vaginal gel formulations of tenofovir, both of which were developed by Gilead Sciences, Inc. In 2006, Gilead assigned rights for the gel to CONRAD and the International Partnership for Microbicides of Silver Spring, Md.

Tenofovir, known by the brand name Viread®, is an ARV commonly used in the treatment of HIV. It belongs to a class of ARVs called nucleoside/nucleotide 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. Tenofovir and Truvada, a combination tablet that contains tenofovir plus emtricitabine, have each been evaluated in clinical trials to determine if they can prevent HIV in people who are HIV-negative, an approach known as oral pre-exposure prophylaxis, or PrEP. The Partners PrEP Study, which evaluated the safety and effectiveness of both tenofovir and Truvada among heterosexual couples in which one of the partners has HIV, found tenofovir used daily reduced the risk of HIV by 67 percent compared to a placebo. (Partners PrEP found that Truvada reduced HIV risk by 75 percent.) Tenofovir was found not to be effective in VOICE, however, after a routine review of study data by an independent group of experts determined that while it was safe among the women in the study, it was no better than the oral placebo tablet in preventing HIV. Unlike in Partners PrEP, the women in VOICE were younger and many were not married or in a committed relationship. Results are not yet available from the Bangkok Tenofovir Study, which involved 2,400 injection drug users in Thailand.

Tenofovir gel is a vaginal microbicide that contains the same active ingredient as the oral tablet formulation of tenofovir. Microbicides are products designed to prevent or reduce the sexual transmission of HIV when applied topically on the inside of the vagina or rectum. In the CAPRISA 004 Phase IIb study, tenofovir gel used before and after sex resulted in 39 percent fewer HIV infections compared to a placebo gel. FACTS 001, which is an ongoing Phase III trial testing the same regimen, hopes to replicate the results of CAPRISA 004. Meanwhile, VOICE stopped testing the gel after an interim review of data determined that it was safe but not effective among the women who were asked to use the gel daily.

7. How does MTN-001 relate to VOICE?
MTN-001 and VOICE were each designed to answer specific questions about tenofovir gel and oral tenofovir but also to help inform and better understand the results of each study. While MTN-001 examined differences

in how the drug is absorbed in blood and vaginal tissue as well as women's preferences for each regimen, VOICE was designed to test the safety and effectiveness of tenofovir gel and oral tenofovir – as well as oral Truvada – and how well women adhere to daily use of either the gel or tablet regimens. Together, MTN-001 and VOICE will provide a more complete picture about each approach.

8. How was MTN-001 designed?
MTN-001 was a Phase II trial designed to evaluate women's adherence to three daily regimens – tenofovir gel, tenofovir tablet and the two together – and the pharmacokinetics of each approach. Pharmacokinetic studies are conducted to learn how a particular drug is absorbed by and distributed in the body over time. Researchers enrolled 168 sexually active, HIV-negative women; 144 participants completed the study. Participants followed each regimen for six weeks, with one week between each study period when no study product was used. At the four U.S. sites, participants were involved in more intensive assessments of each approach.

Adherence: At the three-week midpoint and end of each study period, researchers asked a series of questions to assess participants' experiences using the product regimen, how sexual activity may have changed, how well they adhered to the regimen and the reasons given for not always using the product – did they forget, dislike using it or give the tablet or gel to other people? In addition, a total of 36 women were randomly selected from the three African sites and two of the U.S. sites to take part in in-depth interviews at the end of the 21-week study to elicit more detailed information about their adherence to and preferences for oral and vaginal formulations and the single and dual-use regimens.

Drug absorption and distribution: Researchers measured the concentration of tenofovir in vaginal tissue and blood in both its inactive and active states. To work against HIV, tenofovir must be activated by the addition of two molecules called phosphates, a process that takes place inside the cell. At each mid-study period, participants provided a small amount of blood to determine how much tenofovir was circulating in the body. At sites with laboratory capacity, blood was also used to determine if tenofovir was present inside cells and, if so, how much of the drug was active. At the end of each study period, researchers took samples of blood and vaginal fluid, which was used to look for protective proteins and cytokines, molecules that are part of the body's immune system. Blood and vaginal fluid also was collected within a certain number of hours of the participant taking the dose in the clinic. For the more intensive studies conducted at the U.S. sites, women were randomized into one of four groups based on the schedule of tests performed at the end of each study period. One of these four groups had vaginal fluid, cervix cells and vaginal tissue samples taken before using the product. The three other groups of women underwent these procedures at either two, four or six hours following product use.

9. Why compare a vaginal gel with an oral tablet in the same trial?
Evaluating both approaches in a single trial can yield more scientifically valuable and reliable information with which to directly compare tenofovir gel and oral tenofovir as prevention approaches for women. In MTN-001, critical questions about adherence, acceptability, and pharmacokinetics could be addressed more definitively than separate studies could. For instance, because women in MTN-001 used each of the three daily regimens, they were better able to inform researchers about their preferences for and adherence to each.

10. Why were the studies different in the U.S. and African sites?
Some of the tests and studies that were conducted in MTN-001 required highly specialized clinical facilities and laboratory equipment as well as an experienced staff trained in using them. The U.S. sites had this capacity, which is why the intensive drug studies were performed there.

11. What was done to ensure the safety of the participants?
MTN-001 was designed according to the most rigorous international medical practice and ethical standards and included numerous measures, beginning at the site level, intended to protect the safety and well-being of participants. As with all MTN studies, MTN-001 incorporated a multi-tiered safety review process that involved strict national and international procedures for monitoring and reporting. This process included clinicians evaluating participants at the trial sites; a team at the MTN statistical and data management center (SDMC) that assessed incoming reports on a daily basis; three MTN physicians – two specializing in infectious

diseases and HIV and the other in obstetrics and gynecology – who reviewed summary reports and any concerns raised by site clinicians or the SDMC; monthly reviews by a protocol safety review team; and periodic reviews by a study monitoring committee (SMC). No concerns with safety were found in any of the SMC reviews of MTN-001. Had there been, the SMC could have recommended that the study proceed with design modifications or be discontinued.

12. Did any of the participants acquire HIV while taking part in this trial?
No participants in MTN-001 acquired HIV while they were in the study. To reduce the risk of HIV in women participating in any of its trials, MTN researchers provide all trial participants free condoms, frequent HIV testing and HIV risk-reduction counseling and routine testing and treatment for sexually transmitted infections (STIs). If a woman had become infected during MTN-001, she would have been counseled and referred by study staff to services at local facilities that provide medical care and treatment, including ARV therapy, and psychological and social support.

13. Did women participating in the study provide informed consent?
Written informed consent was obtained from each study participant prior to screening and enrollment using forms translated into local languages. In addition, site community educators and Community Advisory Board members played important roles in helping prospective participants understand the study. The process ensures that women understood the procedures, as well as possible risks and benefits of the study. Participants were told that they were under no obligation to participate and could leave the study at any time, without consequence.

14. What were the medical benefits for women participating in the study?
Study participants received free laboratory tests and physical exams, counseling on HIV prevention and free condoms. STI risk-reduction counseling, testing and treatment was provided at no charge to both women and their partners. In addition, MTN-001 provided pregnancy testing at every clinic visit and linked participants with services related to contraception.

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For more information about MTN-001 go to http://www.mtnstopshiv.org/news/studies/mtn001. Information about VOICE and other MTN studies can be found at http://www.mtnstopshiv.org/news

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