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QUESTIONS AND ANSWERS

MTN-001

Adherence and Drug Absorption Study of Oral and Vaginal Gel Preparations of Tenofovir

1. What was the aim of MTN-001?

MTN-001 was a Phase II trial that directly 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, also hold promise for preventing HIV, particularly in women. MTN-001 was designed to address specific questions about daily use of tenofovir gel and the oral tablet. Its findings will have added relevance when results from a study known as VOICE – Vaginal and Oral Interventions to Control the Epidemic – are available in 2013. VOICE is a large-scale effectiveness study of tenofovir gel, oral tenofovir as well as oral Truvada® enrolling 5,000 women in southern Africa. Taken together, MTN-001 and VOICE will help to understand which approach – and at which dose – is optimal for protecting against HIV.

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. Where was MTN-001 conducted?

MTN-001 was conducted at seven sites in the U.S., 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, the study was conducted at the Umkomaas and Botha's Hill clinical research sites affiliated with the Medical Research Council of South Africa in Durban.

4. What did the study find?

In tests to determine how much active drug is taken up in the body, MTN-001 researchers found that daily use of the vaginal gel achieved a more than 100-times higher concentration of active drug in vaginal tissue than did the oral tablet. Compared to the gel, the tablet used daily was associated with a 20-times higher concentration of active drug in blood. MTN-001 found 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 the gel and tablet were used together. Vaginal itching and irritation were the most common side effects with the gel. According to self-reports, women were able to follow each regimen equally well.

When asked if they would consider using any of the products in the future, 93 percent said they would be likely to use the oral tablet and 83 percent said they would be likely to use the gel. Among only the U.S. women, 87 percent said they would be likely to use the oral tablet and 64 percent, the gel. Interestingly, when African participants were asked about the gel and the tablet, the response was the same for each approach– 100 percent said they would be likely to use either product if it became available. Many African women liked the gel

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because it enhanced sexual pleasure. 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.

5. Why is this study 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. These same approaches are being tested in clinical trials to see if they can prevent HIV in different high-risk populations, including women in sub-Saharan Africa. VOICE – Vaginal and Oral Interventions to Control the Epidemic – is a large-scale effectiveness trial of tenofovir gel, oral tenofovir, as well as Truvada[®], enrolling 5,000 women in southern Africa. Results from MTN-001 will be important to better understand the findings from VOICE, which are expected in 2013. This includes understanding which approach – and at what dose – may be optimal for preventing HIV. Together, MTN-001 and VOICE, will provide a more complete picture about each of the approaches, information that will be essential as regulators consider whether to approve either or both for widespread use.

Six out of 10 new HIV infections in adults occur in women, primarily through unprotected sex with an infected male partner. While male condoms are effective for preventing HIV, women can’t always control their use. In contrast, a vaginal gel and an oral tablet are approaches that women could decide to use, independent of their husband or partner. As the results of MTN-001 already have indicated, there is clear interest in both approaches, but at the same time, women’s preferences differ. No one product or approach will be suitable to all women.

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

The study was launched at the U.S. sites in July 2008 and in Africa, May 2009. It enrolled 168 sexually active, HIV-negative women, with 144 who completed all study visits in the course of the 21 weeks they were in the study. The last of the participants completed the study in July 2010.

7. What products 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., of Foster City, Calif., U.S.. In 2006, Gilead assigned rights for the gel to the International Partnership for Microbicides of Silver Spring, Md., and CONRAD, of Arlington, Va., both of the U.S. For MTN-001, Gilead provided tenofovir tablets free of charge, and CONRAD provided both the gel and gel applicators at no cost.

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), which 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 another ARV called Truvada[®], a combination tablet that contains tenofovir plus emtricitabine, are both being 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. A recent trial called iPrEx found that daily use of Truvada was safe and reduced the risk of HIV by 44 percent among men who have sex with men.

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. 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. Recently, CAPRISA 004, a Phase IIb study conducted in South Africa, found the gel significantly reduced the risk of HIV among at-risk women who were instructed to use it before and after vaginal sex – there were 39 percent fewer HIV infections among women who used tenofovir gel compared to women who used a placebo gel. The U.S. Food and Drug Administration (FDA) has indicated that it will consider approving tenofovir gel as an HIV prevention method for women depending on the results of VOICE, which is testing tenofovir gel used daily. The FDA has also granted the gel Fast Track designation, which allows for its expedited review.

8. 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 is testing the 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 of the approaches, information that will be essential to regulators as they consider whether to approve either or both of the approaches for widespread use.

9. 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.

10. 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.

11. 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 have this capacity, which is why the intensive drug studies were performed there.

12. 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

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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.

13. 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). Despite these intensive, ongoing efforts, a woman participating in a trial could acquire HIV if she has unprotected sex with a partner who is infected. It is important to note that although no participants acquired HIV while in MTN-001, it cannot be assumed from this kind of trial that the products protect against HIV.

14. What would have happened if a participant acquired HIV during the study?

If a woman had become infected during the study, 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. In Africa, study participants who acquire HIV during any MTN study are also invited to participate in 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.

15. Were you concerned that participants in a study like this would feel a false sense of protection and be more apt to engage in high-risk behaviors?

Participants were counseled at each visit on the importance of safe sex practices, including condom use. They were also reminded that neither tenofovir gel nor tenofovir tablet has been proven effective for preventing HIV.

16. Especially in Africa, ARVs are in short supply for HIV-infected individuals. Were you concerned participants would share or sell study products?

Participants were counseled monthly on the importance of adhering to study regimens and the dangers posed by sharing study products with others not in the study. At the same time, MTN-001 was designed to learn as much as possible about the potential that drug sharing or selling could be a problem. These results are still being analyzed. When available, the information will be critical for developing site- and community-level strategies to prevent such practice in future clinical trials and if and when these approaches are widely used.

17. 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.

18. 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 other MTN studies can be found at <http://www.mtnstopshiv.org/news>