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MICROBICIDE TRIALS NETWORK 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 preparations of the antiretroviral (ARV) drug tenofovir, looking at differences in how and where the drug is absorbed in the body and differences in women's adherence to and acceptability of each dosing approach separately and in combination. ARVs are medicines used in the treatment of HIV. ARV-based approaches, such as those studied in MTN-001, hold promise for prevention of HIV as well, particularly for women. Women are most often infected through unprotected sexual intercourse, in part because certain cells in the vagina are receptive targets for the virus. As such, it is important to know how active or potent these approaches are in the cells most likely to be infected. MTN-001 will provide important information about daily use of each formulation of tenofovir and provide insight about women's preferences for and their ability to adhere to each regimen.

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). 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). Craig W. Hendrix, M.D., an associate professor of medicine in the Division of Clinical Pharmacology at Johns Hopkins University in Baltimore, Maryland, led the study. As co-sponsors of MTN-001, CONRAD of Arlington, Virginia, USA; and Gilead Sciences, Inc., of Foster City, California, USA, provided the study products free of charge.

3. Where was MTN-001 conducted?

MTN-001 involved 168 sexually active, HIV-negative women who enrolled at one of seven sites in the United States, Uganda and South Africa. The U.S. sites were Case Western University, Cleveland, Ohio; University of Pittsburgh, Pittsburgh, Pennsylvania; University of Alabama at Birmingham, Birmingham, Alabama; and Bronx-Lebanon Hospital, Columbia University, New York, 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. 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. Each participant was in the study for about 21 weeks. Results of the study are expected to be available early 2011.

5. What is a microbicide?

Microbicides are substances designed to prevent or reduce the sexual transmission of HIV when applied topically inside the vagina or rectum. A microbicide can be formulated in many ways, such as a gel or cream,

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or as a ring that would release the active ingredient over time. Some microbicides are also being developed for rectal use. Several microbicide products are being tested in clinical trials, including trials conducted by the MTN, although none is currently approved or available for use.

6. What products were studied in MTN-001?

MTN-001 studied the tablet and topical vaginal gel preparations of tenofovir. The active ingredient in tenofovir belongs to a class of ARVs called nucleotide/nucleoside 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. In its tablet form, tenofovir disoproxil fumarate, known by the brand name Viread, is approved as a treatment for HIV infection when used in combination with other drugs and is well tolerated by most people. Both oral and vaginal gel formulations of tenofovir were developed by Gilead Sciences, Inc., of Foster City, California, USA, which assigned a royalty-free license for the topical gel to the International Partnership for Microbicides of Silver Spring, Maryland, and CONRAD, of Arlington, Virginia, in December 2006. For MTN-001, Gilead provided tenofovir tablets free of charge, and CONRAD provided both the gel and gel applicators at no cost.

Tenofovir gel: Tenofovir gel is a candidate microbicide being evaluated for its potential ability to prevent the sexual transmission of HIV. Laboratory and animal studies have demonstrated that tenofovir gel can prevent HIV infection of target cells in vaginal tissue. Clinical safety studies performed to date indicate it is well tolerated and safe in both HIV-positive and HIV-negative women. Results from an expanded safety and acceptability trial called HPTN 059 found daily use of the gel over six months was safe in and well-tolerated by sexually active HIV-negative women.

Tenofovir tablet: Tenofovir is being evaluated in clinical trials to determine if this first-line drug for treatment can also prevent HIV when used by people who are HIV-negative, an approach known as pre-exposure prophylaxis, or PrEP. Thus far, the limited number of PrEP studies suggests the drug is safe to be used in trials of people without HIV. A study conducted by Family Health International in 936 HIV-negative women in Ghana, Cameroon and Nigeria, found no serious side effects in women who took tenofovir for up to one year, although some participants noted stomach discomfort and headache. Participants in MTN-001 were given the same dose of tenofovir used for treating HIV.

8. Why is this study important?

As the field moves to explore the promise of ARV-based prevention methods, it is especially important to understand how different ARV formulations, such as a vaginal gel or oral tablet, are taken up by the body and which approach, and at what dose, is optimal for achieving drug concentrations likely to prevent HIV. Understanding how and why women are willing or able to commit to a particular formulation also is vital to the development of safe and effective prevention strategies, because not even the best approach can be effective if women don't use it. Until MTN-001, no trial had ever evaluated oral tablet and vaginal gel formulations of tenofovir in the same study. As such, MTN-001 was designed to address key questions to help inform ongoing and planned trials, including VOICE (Vaginal and Oral Interventions to Control the Epidemic). Both studies come at a critical time: women account for nearly half of the more than 33 million people living with HIV/AIDS worldwide, and between 70 and 90 percent of all HIV infections in women are due to heterosexual intercourse. Women desperately need a method for preventing HIV that they can control themselves. Indeed, the full array of HIV prevention strategies in the future may include oral or vaginal gel formulated agents or combinations of these, which is why MTN-001 evaluated daily regimens of the tablet, the vaginal gel and the two combined.

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. Participants followed each regimen for six weeks, with one week between when no study product was used. At the four U.S. sites, the 86 women enrolled were involved in more intensive assessments of each approach.

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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? A small number of participants from each site also took part in in-depth interviews at the end of the 21-week study to elicit more detailed information about women's adherence to and preferences for oral and vaginal formulations and the single and dual-use regimens.

Drug absorption and distribution: Researchers wanted to look at how the drug is absorbed and how much of it is in its activated state over time through tests of blood plasma (the liquid component of blood), white blood cells, vaginal tissues, and cells taken from inside the vagina. At each mid-study period, participants provided a small amount of blood to determine how much tenofovir was circulating in the blood. Where sites have laboratory capacity, blood was also used to determine if tenofovir was present inside blood cells and, if so, whether the drug was in its active or inactive state. At the end of each study period, participants followed their assigned regimen at the clinic, and similar tests were conducted. First, 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 1-3 hours, 3-5 hours or 5-7 hours after the in-clinic dose, depending on which time interval had been randomly chosen for the participant. For the more intensive studies conducted at the U.S. sites, the 86 women were randomized into one of four groups to determine the schedule of tests performed at the end of each study period. All four groups of women had blood drawn before and at one-, two-, four-, six- and eight-hour intervals following the use of their assigned gel and/or tablet regimen. One of the 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 gel with a pill in the same trial?

Evaluating both approaches in a single trial is the most expeditious research avenue for yielding the most valuable and reliable information with which to directly compare tenofovir gel and oral tenofovir as prevention for women. In MTN-001, critical questions about adherence, acceptability, and pharmacokinetics can be addressed more definitively than separate studies could. For instance, because women in MTN-001 experienced using each of the three daily regimens, they will be able to better inform researchers about their preferences for and adherence to each. As well, MTN-001 can discern more clearly the differences between each formulation in order to achieve optimal concentrations of the drug for prevention.

11. Is there a difference between the drug in the tablet and gel forms of tenofovir?

As chemical structures, oral tenofovir and the tenofovir drug used in the gel are not exactly alike. In tablet form, tenofovir disoproxil fumarate has two additional molecules that improve its absorption from the gastrointestinal tract after oral dosing. Tenofovir gel has the advantage of being applied at the site of infection, potentially achieving higher local concentrations where it is needed most, thereby limiting exposure to the rest of the body and the risk of drug side effects. For either formulation of tenofovir to have anti-HIV activity inside targeted cells, the drug must still be activated by the addition of two molecules called phosphates.

12. Why were the studies different in the US and African sites?

Some of the tests and studies that were conducted in MTN-001 require 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.

13. How does this trial differ from other microbicide trials?

MTN-001 was the first trial of both oral and gel formulations of tenofovir and the first to directly compare each regimen on parameters related to adherence, acceptability and how the drug in each formulation is absorbed by the body.

14. How could a woman acquire HIV while taking part in this trial?

To reduce the risk of HIV for 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.

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15 What happened if a participant acquired HIV during the study?

A woman who had become infected during the study, would be 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. MTN-015 is a long-term observational study of women who acquire HIV during an MTN trial that seeks to understand the nature of HIV progression and treatment response.

In MTN-015, women make frequent visits to the research site for physical exams and laboratory tests that help researchers assess how the disease is progressing and how the women are responding to treatment. 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

16. Does MTN provide ART to women who acquire HIV?

MTN receives funding to conduct clinical trials only and, therefore, is not adequately resourced to provide HIV treatment, including antiretroviral treatment (ART). However, MTN investigators have given a great deal of thought to the issue of providing ART to women who acquire HIV during study participation. Any participant who may have acquired HIV during MTN-001 would have been linked with appropriate services and care in the study site communities.

17. Because women in this study were using ARV-based products, was there concern about drug resistance?

It's important to understand that drug resistance would be possible only in someone infected with HIV, and MTN-001 worked to reduce the risk of HIV infection in all women who participated. If, despite the study's efforts a woman became infected, safeguards were in place to minimize the potential for drug resistance. For instance, women were tested for HIV every three weeks. If a test had indicated that a woman acquired HIV, staff would have immediately stopped her use of study product, because its continued use could increase the chance that virus will become resistant to the drug. Some experts believe HIV drug resistance in the context of prevention will be much less prevalent than it is in the treatment setting. But until more information is available, the potential risks are not known.

18. 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 adhering to the regimens of the study and on safe sex practices, including condom use. They were also reminded that neither tenofovir gel nor tenofovir tablet is proven to be effective for preventing HIV.

19. 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 of drug sharing or selling could be a problem. When results are available, this information will be critical for developing site- and community-level strategies aimed at preventing such practice in future clinical trials and if and when ARV-based strategies are widely used.

20. 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 assesses incoming reports on a daily basis; two MTN physicians – one 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.

21. 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.

22. What were the medical benefits for women participating in the study?

Study participants received free laboratory tests and physical exams, counseling on preventing HIV infection 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. If a participant acquired HIV during the trial, they were counseled appropriately and received referrals to community-based programs for care and support. In addition, they were asked to remain in the trial off of study product and be followed with all scheduled safety evaluations.

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More information about MTN-001 and other MTN studies can be found at <http://www.mtnstopshiv.org/news>

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