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BACKGROUNDER

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

Overview

MTN-001 was a Phase II trial that directly compared the oral tablet and vaginal gel formulations of the antiretroviral (ARV) drug tenofovir. Specifically, MTN-001 evaluated women's adherence to and acceptance of 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 at seven sites in Uganda, South Africa and the U.S., who were asked to follow each regimen for six weeks, with one week between each study period when no study product was used. Of the 168 women, 144 completed all study visits, including 72 women enrolled at the four U.S. sites who were involved in more intensive assessments of each approach. The study was launched at the U.S. sites in July 2008 and in Africa, May 2009. The last of the participants completed the study in July 2010. Results were reported February 2011 at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, U.S.

MTN-001 was 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) of 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). MTN-001 itself was funded by NIAID/DAIDS. Craig W. Hendrix, M.D., of Johns Hopkins University, led the study.

What the Study Found

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 more than 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 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.

Why MTN-001 is 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

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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, MTN's flagship trial, 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.

How the Study Was Conducted

MTN-001 was a Phase II trial that examined differences in how tenofovir is absorbed in blood and vaginal tissue when delivered as a vaginal gel or orally as a tablet, as well as women's preferences for and ability to follow each daily regimen. All participants used each product daily for six weeks, as well as the two together, with one week between each study period when no study product was used.

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 so that researchers could 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 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 some sites, blood was also used to determine if tenofovir was present inside cells and, if so, whether the drug was in its active or inactive state. 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. For the more intensive studies conducted at the U.S. sites, researchers looked also at cervix cells and vaginal tissue samples.

The Products Studied

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 help 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 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. In the CAPRISA 004 study, there were 39 percent fewer infections among women who used tenofovir gel before and after sex compared to women who used a placebo gel. In VOICE, women are using gel daily, regardless of when they have sex. 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. The FDA has also granted the gel Fast Track designation, which allows for its expedited review.

Both oral and vaginal gel formulations of tenofovir were developed by Gilead Sciences, Inc., of Foster City, Calif., U.S., which assigned rights for the topical gel to the International Partnership for Microbicides of Silver Spring, Md., and CONRAD, of Arlington, Va., 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.

Participant Safety and HIV Monitoring

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.

Participants were counseled at each visit that neither tenofovir gel nor tenofovir tablet has been proven effective for preventing HIV. To reduce the risk of HIV in women in the study, researchers provided free condoms, frequent HIV testing and HIV risk-reduction counseling, including on the use of condoms, and routine testing and treatment for STIs. No participants in MTN-001 acquired HIV while in the study. Should this have happened, they 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 in any MTN study are invited to participate in MTN-015, a long-term observational study that seeks to understand the nature of HIV progression and treatment response.

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

About the Microbicide Trials Network

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners who are devoted to preventing or reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.

28-February-2011