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Understanding the Results of MTN-001

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

MTN-001 was the first study to directly compare the vaginal microbicide tenofovir gel and the oral tablet formulation of tenofovir, an antiretroviral (ARV) drug commonly used in the treatment of HIV. Tenofovir gel and the oral tablet are promising approaches for preventing HIV in women. MTN-001 has provided important insight about how tenofovir is taken up in the body when formulated as either a tablet or a vaginal gel and on women's preferences for each when used daily. The findings, which were reported at the 2011 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, U.S., will have added relevance when results from a study known as VOICE are available, in 2013. VOICE – Vaginal and Oral Interventions to Control the Epidemic – is a large-scale trial testing the safety and effectiveness of these regimens, 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.

SUMMARY

- **MTN-001 was the first study in which head-to-head comparisons were made between tenofovir gel and oral tenofovir, two promising approaches for preventing HIV in women.** The study, which involved 144 women in the U.S. and Africa, examined differences in how the drug is absorbed in blood and vaginal tissue as well as women's preferences for each daily regimen.
- **Preferences for the vaginal gel and tablet differed among U.S. and African women.** Most women in the U.S. favored the tablet more than the gel, while African women in the study favored use of the gel and the tablet equally. Many of the African women liked the gel because it enhanced sexual pleasure.
- **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**, while, compared to the gel, the tablet used daily was associated with a more than 20-times higher active drug concentration in blood. These results do not necessarily define where the drug needs to be or how much is needed to protect against HIV transmitted through vaginal sex, however.
- **MTN-001 was not designed to determine whether tenofovir gel or the tablet is effective for preventing HIV. But its results will add important insight to a large trial that *is.*** VOICE is an ongoing, large-scale effectiveness trial of tenofovir gel, oral tenofovir, as well as Truvada, that is expected to have results in 2013. Information from MTN-001 and VOICE will be essential as regulators consider whether to approve either or both of the approaches for widespread use.
- **In sub-Saharan Africa, 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 in 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.

BACKGROUND

MTN-001

- MTN-001 was a Phase II trial that directly compared tenofovir formulated as a vaginal gel and as an oral tablet. Researchers examined how the drug is absorbed in vaginal and cervical tissue and in blood and women's preferences for and ability to follow daily regimens of each. The study involved 144 women, evenly divided between the U.S., and Uganda and South Africa. All women in the study used each product daily for six weeks, as well as the two together. The study was launched at the U.S. sites in July 2008 and in Africa in May 2009. The last of the participants completed the study in July 2010.

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- All three daily regimens (vaginal gel, oral tablet and the two combined) were safe in and 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 of the participants said they would be likely to use the oral tablet and 83 percent said they would be likely to use the gel. Among only 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. 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 said they liked them both equally. Many of the African women said they liked the gel because it enhanced sexual pleasure.
- Researchers measured the concentration of tenofovir in vaginal tissue and blood in both its inactive and active states. Tenofovir must be in its active state to work against HIV, a process that occurs inside a cell with the addition of two molecules called phosphates. Use of the vaginal gel achieved a more than 100-times higher concentration of active drug in vaginal tissue compared to the oral tablet. The concentration of active drug in the blood was more than 20-times higher with the oral tablet than with the gel.
- 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 (NIMH) 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 and study products were donated by CONRAD of Arlington, Va., U.S., which provided the gel and applicators; and Gilead Sciences, Inc., of Foster City, Calif., U.S., which provided the tablets. Craig W. Hendrix, M.D., of Johns Hopkins University, led the study.
- The study took place at seven MTN-affiliated clinical research sites – four in the U.S. and three in Africa. In the U.S., study 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. The three African sites are also conducting VOICE.

VOICE

- VOICE is a Phase IIb trial designed to evaluate both the safety and effectiveness of two approaches for preventing HIV through vaginal sex: daily use of an ARV tablet (tenofovir or Truvada) and daily use of an ARV-based gel (tenofovir gel). VOICE is the first effectiveness study of a microbicide that women use every day. It is also the only trial evaluating both a tablet and a gel in the same study, which is important for measuring how each product works compared to its control (placebo gel or placebo tablet) and determining which approach women may prefer.
- VOICE is being conducted at 15 clinical research sites in South Africa, Uganda and Zimbabwe. The study began in September 2009 and is expected to take about three and a half years to complete, with results due in early 2013. VOICE will involve approximately 5,000 women who are randomized into one of five study groups – tenofovir tablet, Truvada tablet, placebo tablet, tenofovir gel and placebo gel – with about 1,000 in each. Already, more than 3,000 women have enrolled. Participants use their assigned study product every day for the duration of the study, about two years on average. Women in VOICE receive ongoing HIV risk-reduction counseling, condoms, and diagnosis and treatment of STIs – all proven measures for reducing the risk of HIV.

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- VOICE is MTN's flagship study and the centerpiece in a portfolio of trials focused on tenofovir gel. These include the only studies looking at its safety in women who are pregnant or breastfeeding as well as its safety when used rectally. VOICE is funded by NIAID/DAIDS and NIMH, both of the NIH. As co-sponsors of VOICE, CONRAD and Gilead Sciences are providing the study products free of charge. VOICE is being led by Zvavahera Mike Chirenje, M.D., University of Zimbabwe in Harare; and Jeanne Marrazzo, M.D., M.P.H., University of Washington, Seattle, U.S.

THE ARVs BEING TESTED IN ARV-BASED PREVENTION TRIALS

- **Tenofovir**, also known by the brand name Viread®, and **Truvada,** the brand name for a combination drug that contains both tenofovir (or TDF, for short) and emtricitabine (FTC), are oral drugs approved for the treatment of HIV when used in combination with other ARVs as part of a regimen called antiretroviral therapy. Both drugs, which are marketed by Gilead Sciences, are being evaluated in clinical trials to determine if they also 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 was safe and reduced the risk of HIV by 44 percent among men who have sex with men. There are currently eight ongoing trials testing these drugs as oral PrEP in different at-risk populations, including four large-scale effectiveness studies. While most studies are testing either tenofovir or Truvada, only VOICE and the Partners PrEP Study are evaluating both. The Partners PrEP Study involves 4,700 serodiscordant couples – in which one partner is HIV infected and the other is not – in Kenya and Uganda.
- **Tenofovir gel** contains the same ingredient that is in oral tenofovir. 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. Tenofovir gel was developed by Gilead Sciences, which assigned the rights for the gel to CONRAD and the International Partnership for Microbicides (IPM) of Silver Spring, Md., U.S., in 2006.

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Additional information about MTN-001 is available at http://www.mtnstopshiv.org/news/studies/mtn001; additional information about VOICE is available at http://www.mtnstopshiv.org/news/studies/mtn003

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.

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