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BACKGROUNDER

MTN-008
Expanded Safety Study of Tenofovir Gel in Pregnant and Breastfeeding Women

Study Overview

MTN-008 was a Phase I study designed to determine whether using a vaginal microbicide called tenofovir gel daily for one week is safe for women late in pregnancy and while breastfeeding. MTN-008 is part of a comprehensive research program established to take incremental steps toward determining whether tenofovir gel can safely and effectively protect women against HIV during all stages of pregnancy and motherhood. Tenofovir gel, which contains an antiretroviral (ARV) drug commonly used to treat people with HIV, has been evaluated in several studies as a potential product for HIV prevention. This was the first clinical trial of tenofovir gel conducted among breastfeeding women.

The study was a follow-up to MTN-002, which found that a single dose of tenofovir gel given to pregnant women hours before scheduled Cesarean delivery was safe and well-tolerated by both mother and infant. In MTN-008, researchers evaluated the safety of tenofovir gel and assessed how much active drug was absorbed in the last trimester of pregnancy and subsequently transferred to the fetus. Researchers also measured drug levels in breast milk of breastfeeding mothers and assessed whether the drug was transferred to the baby. The study involved 91 pregnant women – 45 women at 37 weeks gestation and 46 women at 34 weeks gestation; and 16 women who were breastfeeding. Results are expected before the end of 2014.

MTN-008 was conducted at Magee-Womens Hospital of the University of Pittsburgh Medical Center and the University of Alabama, Birmingham (UAB), through the Microbicide Trials Network (MTN), a clinical trials network established and funded in 2006 by the Division of AIDS at 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 (NICHD), all components of the U.S. National Institutes of Health. Richard Beigi, M.D., M.Sc., of the University of Pittsburgh School of Medicine and Magee-Womens Hospital, led the study.

Why this Study is Important

Women represent more than half (52 percent) of all people living with HIV worldwide and account for nearly 60 percent of those with HIV in sub-Saharan Africa. Most of these women acquired HIV from unprotected vaginal sex. Microbicides are products applied inside the vagina or rectum to protect against HIV though sex, and are being developed primarily for use by sexually active women. Yet, there is very little information about whether these products can be safely used by pregnant and breastfeeding women, most of whom remain sexually active and continue to be at risk for HIV. In fact, some studies suggest that women may be particularly susceptible to HIV during pregnancy due to heightened immune responses or hormonal changes that affect the mucosal lining in the vagina. Because women often continue to use medications during pregnancy, knowing whether microbicides are safe to use in this population also is vitally important.

Tenofovir gel is currently being evaluated in an ongoing Phase III trial called FACTS 001 looking to see if it is safe and effective among women who use it before and after sex. The same regimen was found to reduce the risk of HIV among women in the CAPRISA 004 study. Tenofovir gel was not effective in the VOICE study, however, which was designed to evaluate its daily use (as well as daily use of either the oral ARV tablet tenofovir or Truvada®), possibly because most of the women in VOICE did not use their assigned products as instructed. Meanwhile, results of FACTS 001 are expected late 2014 or early 2015, and if the gel is found to be effective – when used around sex – CONRAD, as co-licensee of the product, plans to seek its regulatory

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approval. As such, MTN-008 will provide critical information about the safety of tenofovir gel during pregnancy and lactation.

How the Study was Conducted

MTN-008 was a Phase I expanded safety study looking at daily use of tenofovir gel for one week by pregnant women in the third trimester of pregnancy, and the daily use of the gel for one week by breastfeeding mothers four to 26 weeks after they have given birth. The study included 107 HIV-negative mother-infant pairs (91 pairs in the pregnancy group and 16 pairs in the nursing group). The tests and procedures performed as part of the study included urine and blood tests, vaginal and cervical fluid collection, and pelvic and physical examinations to determine how the drug was absorbed and distributed in the body. Once a woman gave birth, researchers also measured the presence of the gel's active ingredient in the umbilical cord blood. For the group of breastfeeding women, the presence of active drug was measured in breast milk and in blood samples from both mother and infant.

The Product Studied

MTN-008 evaluated tenofovir formulated as a vaginal gel. Tenofovir 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 in order to take over a host cell. Each dose of tenofovir gel contains approximately 40 mg of active drug. Both the tablet and gel forms of tenofovir were developed by Gilead Sciences, Inc., of Foster City, Calif., U.S. In 2006, Gilead assigned a royalty-free license for tenofovir gel to CONRAD of Arlington, Va., and the International Partnership for Microbicides of Silver Spring, Md.

Participant Safety

MTN-008 was designed according to the most rigorous international medical practice and ethical standards and includes numerous measures to protect the safety and well-being of participants. As with all MTN studies, MTN-008 incorporated a multi-tiered safety review process. This process included clinicians evaluating participants at the trial sites; a team at the 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 review by a study monitoring committee. MTN-008 was reviewed by the Institutional Review Boards (IRBs) at the University of Pittsburgh and UAB, to ensure that it was scientifically valid and ethically conducted. Written informed consent was obtained from all participants prior to enrollment to ensure they understood the procedures, as well as possible risks and benefits of the study.

Funding

MTN-008 was funded by NIAID and NICHD. CONRAD provided tenofovir gel and the gel applicators.

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More information about MTN-008 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 whose work is focused on the development and rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org.

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