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MICROBICIDE TRIALS NETWORK BACKGROUND

MTN-002: PHASE I STUDY OF TENOFOVIR GEL IN PREGNANCY

Study Overview

MTN-002 was the first study of a candidate topical microbicide ever to be conducted in pregnant women. Microbicides are products being designed for use in sexually active women of reproductive age to prevent or reduce the sexual transmission of HIV or other sexually transmitted infections when applied topically on the inside of the vagina. MTN-002 sought to understand if and to what extent pregnancy affects how the body absorbs the active drug in a gel and whether the drug can be transferred to the fetus. Specifically, MTN-002 researchers examined an antiretroviral-based candidate microbicide called tenofovir gel, which was applied as a one-time, single dose in 16 healthy HIV-negative women prior to giving birth by scheduled caesarean delivery. Women are twice as likely as their male partners to acquire HIV during sex, due in part to biological factors that make them more susceptible. Recent studies now suggest that pregnancy is a time when women may be at even greater risk for acquiring HIV through sexual intercourse. Researchers conducted MTN-002 as a first step toward determining if use of a vaginal microbicide during pregnancy is safe for women and their babies. The study enrolled its first participants in August 2008 and was completed in January 2010. Results were announced in May 2010.

The study was conducted at Magee-Womens Hospital of the University of Pittsburgh Medical Center 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 (NIH).

What the Study Found

MTN-002 found only small amounts of drug are absorbed into the mother's bloodstream, amniotic fluid and umbilical cord (fetal) blood. Compared to studies looking at single-dose (600 mg) oral tenofovir for preventing mother-to-child transmission of HIV, the amount of drug found in umbilical cord blood after a 40-mg single dose of tenofovir gel was 40 times lower – 1.93 nanograms per milliliter (ng/ml) versus 76 ng/ml. The median drug levels found in maternal blood were 50 to 100 times lower than with oral dosing, 4.3 ng/ml compared to 448 ng/ml. Moreover, the amount of drug absorption seen in the pregnant women in this study was remarkably similar to absorption levels after one application of tenofovir gel in nonpregnant women. At 0.53 ng/ml, the median drug levels detected in the amniotic fluid were also small and less than what has been seen with the oral drug. Importantly, there were no serious side effects attributed to the gel in either the mothers or their newborns within the first two weeks of life, the time during which researchers were collecting information. While analysis of some of the data is still to be completed, based on what is known of the results at this time, the researchers plan to conduct a larger study of tenofovir gel involving both pregnant and breastfeeding women.

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Why this Study is Important

MTN-002 has provided critical information in an area where none existed before, and it will serve as a foundation for building greater understanding about whether microbicide use during pregnancy is safe for women and their babies. The study was not about a single candidate microbicide per se; it was a study that intended to inform an entire field of microbicide research. MTN-002 represents an important first step toward realizing the needs of women who require safe and effective methods for preventing HIV and assurance in knowing that these methods will be safe to use during pregnancy as well. Between 70 and 90 percent of all HIV infections in women are acquired through heterosexual intercourse, and women are twice as likely as their male partners to acquire HIV during sex, due in part to biological factors that make them more susceptible. Many women remain sexually active during pregnancy, when the risk of acquiring HIV doubles, according to a large prospective study conducted by a Johns Hopkins University-led team in Uganda. The authors hypothesized that this increased risk during pregnancy may be due to heightened immune responses or hormonal changes affecting the genital tract's mucosal lining. These and other studies point to the need for safe and effective methods to protect both mothers and their babies against HIV.

Tenofovir gel has already entered into large-scale Phase IIb effectiveness trials. CAPRISA 004 has just been completed, and VOICE – Vaginal and Oral Interventions to Control the Epidemic, an MTN study involving 5,000 women in southern Africa, is underway. Parallel evaluations in pregnant women demonstrating safety could potentially allow women who become pregnant during effectiveness trials to continue using the study product. Moreover, if tenofovir gel or any other microbicide were to become widely available, pregnant women likely will be among those using the product. Evaluating safety in this population before any product is marketed is important to ensure that microbicides are used by as many women as can safely benefit. Indeed, a recent Institute of Medicine report on the methodological challenges in HIV prevention trials included among its key recommendations the need for evaluating the potential effects products may have on pregnant women and their fetuses.

How the Study Was Conducted

MTN-002 was a Phase I study that looked at the pharmacokinetics and placental transfer of tenofovir gel in pregnant women who received a single vaginal dose of tenofovir gel approximately two hours prior to cesarean (C-section) deliveries. Researchers conduct pharmacokinetic studies when they want to learn how a particular drug is absorbed by and distributed in the body. In MTN-002, researchers examined and measured the presence of the gel's active ingredient in the woman's blood and uterus; the baby's placenta and umbilical cord blood; and in the amniotic fluid surrounding the baby. To do this, the researchers drew blood samples from the mother before and at specific time points up to 24 hours after the gel was applied. A sample of the amniotic fluid will be collected during the C-section prior to delivery of the baby. An umbilical cord blood sample and a small piece of the placenta were obtained after delivery. A small piece of tissue from inside the uterus was also collected. Researchers monitored the status of newborns while they remained in the hospital. Women were examined by a study physician 24 hours after receiving the study gel and contacted two weeks later to see how they and their babies were doing.

The Candidate Microbicide Studied

MTN-002 evaluated the candidate vaginal microbicide topical tenofovir gel. Its active ingredient, tenofovir, belongs to a class of antiretroviral (ARVs) drugs called nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), which act against HIV by targeting a key enzyme the virus needs to copy itself before taking over a host cell. In its oral 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. In its current formulation, each dose of tenofovir gel contains approximately 40 mg of active drug. Both oral tenofovir and tenofovir gel 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.

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Preclinical studies have demonstrated that tenofovir gel can prevent HIV infection of vaginal tissue. Clinical safety studies performed to date indicate it is well-tolerated and safe in both HIV-positive and HIV-negative women. Recent results from an expanded safety and acceptability trial called HPTN 059 found the gel was safe in sexually active HIV-negative women when used every day for six months. No studies of the gel had been conducted in pregnant women until MTN-002. Oral tenofovir, however, is being studied in HIV-infected women late in pregnancy for its potential to prevent mother-to-child transmission of HIV. In a study conducted by the NIH-funded International Maternal, Pediatric, and Adolescent AIDS Clinical Trials Group, researchers have thus far seen no significant side effects or problems among women and infants following a 600 mg oral dose of tenofovir given either at the onset of labor or four hours before scheduled cesarean delivery.

Participant Safety

MTN-002 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-002 incorporated a multi-tiered safety review process for monitoring and reporting. 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; two MTN physicians – one specializing in infectious diseases and HIV and the other in obstetrics and gynecology – who review 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-002 researchers would not have conducted this study without evidence that tenofovir gel was safe to evaluate in pregnant women. Earlier safety studies of tenofovir gel showed that a small amount of the drug in tenofovir gel is absorbed into the blood from the vagina, an amount equivalent to only about 1 percent of the amount absorbed from the oral tablet. The Antiretroviral Pregnancy Registry has collected information on more than 700 HIV-infected women who received treatment with oral tenofovir during their pregnancies that shows no differences in birth defects compared to babies whose mothers never took tenofovir. Similarly, in separate studies, researchers have found very low amounts of tenofovir in the babies of mothers who took oral tenofovir during pregnancy, and babies whose mothers took the oral form of tenofovir had no complications or problems that were thought to be related to the drug. The U.S. Food and Drug Administration designates oral tenofovir as a pregnancy category B drug, a classification given to drugs in which animal studies have found no fetal risk.

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MTN-002 is funded by the Division of AIDS, NIAID, and by NICHD, both part of NIH. Tenofovir gel was provided free of charge by CONRAD.

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More information about MTN-002 and other MTN studies is available 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.

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