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## **MICROBICIDE TRIALS NETWORK QUESTIONS AND ANSWERS**

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

#### **1. What was the aim of MTN-002?**

MTN-002 was the first study of a candidate topical microbicide ever to be conducted in pregnant women. As such, it 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 studied 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. Like other candidate microbicides, tenofovir gel is a product being developed to prevent the sexual transmission of HIV in women, who are twice as likely as their male partners to acquire HIV during sex. To date, clinical trials of microbicides primarily have targeted this at-risk population – young women of reproductive age. Now, recent studies suggest that during pregnancy 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.

#### **2. What is a microbicide?**

Microbicides are products designed to prevent or reduce the sexual transmission of HIV or other sexually transmitted infections when applied topically on the inside of the vagina or rectum. A microbicide can be formulated in many ways, such as a gel or cream, or as a ring that would release the active ingredient over time. Several microbicide products are being tested in clinical trials, including trials conducted by the Microbicide Trials Network (MTN), although none is yet approved or available for use.

#### **3. Why is this study important?**

Microbicides, products designed to prevent sexual transmission of HIV, are being developed for sexually active women of reproductive age, yet no study has ever involved pregnant women. As such, 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. A recent Institute of Medicine report on the methodological challenges in HIV prevention trials included among its key recommendations the need to evaluate the potential effects products may have on pregnant women and their fetuses. MTN-002 has provided a framework for ongoing study in this important area.

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

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acquiring HIV doubles, according to a large prospective study conducted by a Johns Hopkins University-led team in Uganda. The authors suggested 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. Realistically speaking, if tenofovir gel or any other microbicide were to become widely available, pregnant women 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.

#### **4. Who conducted and funded MTN-002?**

MTN-002 was conducted by a team of researchers working in the 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 (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). All three institutes are components of the U.S. National Institutes of Health (NIH). The study was led by Richard Beigi, M.D., M.Sc., an assistant professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine. MTN-002 was funded by the Division of AIDS, NIAID; and NICHD.

#### **5. Where and when was the trial conducted?**

MTN-002 was conducted at Magee-Womens Hospital of the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania, USA. The first participants were enrolled in August 2008 and follow-up of all study participants was completed in January 2010 as planned.

#### **6. How was MTN-002 designed?**

MTN-002 was a Phase I study that examined the pharmacokinetics and placental transfer of tenofovir gel in 16 healthy, HIV-negative pregnant women who were scheduled for 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, women received a single vaginal dose containing 40 mgs of tenofovir gel applied approximately two hours prior to cesarean delivery. Researchers then looked to see if and how much of the gel's active drug was in the woman's blood and uterus; the 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.

#### **7. What microbicide was studied in MTN-002?**

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, in December 2006. For MTN-002, both the gel and applicators were provided by CONRAD.

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 have been conducted in pregnant women, other than 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 being 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 15 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.

#### **8. Why was tenofovir gel chosen for this study?**

As an oral drug, tenofovir is increasingly being used during pregnancy, whereas none of the other current ARV-based vaginal microbicides have an oral formula in clinical use, so there is much less information about their track records on safety. Even if other ARV-based microbicides were ahead of tenofovir in their development, tenofovir gel would still be the best choice for current studies in pregnancy because of the large experience using the oral form of the drug. Moreover, 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 demonstrating safety in pregnant women could potentially allow women who become pregnant during effectiveness trials to remain in the study and continue using the product.

#### **9. What were the results of the study?**

MTN-002 found only small amounts of drug are absorbed into the mother's blood, 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 millileter (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 was 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.

#### **10. How did this study differ from other microbicide trials?**

MTN-002 was the first study of a candidate microbicide in pregnant women.

#### **11. What approvals were required to conduct the study?**

The study underwent extensive and rigorous review by NIAID, NICHD, the U.S. Food and Drug Administration and the University of Pittsburgh Institutional Review Board (IRB). IRBs ensure that studies are scientifically valid and ethically conducted and they provide oversight throughout the duration of a trial.

#### **12. Is tenofovir gel safe to give during pregnancy? What about risks to the baby?**

MTN-002 researchers would not have conducted this study without evidence that tenofovir gel was likely to be safe 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 that 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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**13. What about breastfeeding?**

Small amounts of tenofovir appear to cross into the breast milk of breastfeeding women who are taking the oral drug. Researchers currently do not know if tenofovir passes into breast milk after women receive the vaginal form of the drug. Given the amount of drug contained in one dose of the study gel, MTN investigators believe there is little chance of the drug passing into breast milk, and even with trace amounts, the effects on the baby would be negligible. Researchers are currently planning to study the safety of tenofovir gel in mothers and their babies during breastfeeding in an upcoming study called MTN-008.

**14. What was done to ensure the safety of the participants?**

MTN-002 was designed according to the most rigorous international medical practice and ethical standards and includes 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 which included strict national and international standards 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 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.

**15. Did women participating in the study provide informed consent?**

Written informed consent was obtained from each study participant prior to screening and enrollment. The process ensured that women understood the procedures, as well as possible risks and benefits of the study. Participants were under no obligation to participate and were aware that they could leave the study at any time, without consequence.

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More information about MTN-002 and other MTN studies is available at <http://www.mtnstopshiv.org/news> .

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