CONTACTS: Clare Collins
+1-412-641-7299
+1-412-770-8643 (mobile)
collcx@upmc.edu

Lisa Rossi
+1-412-641-8940
+1-412-916-3315 (mobile)
rossil@upmc.edu

QUESTIONS AND ANSWERS

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

1. What was the aim of MTN-008?
MTN-008 was a Phase I study that aimed to find out whether a vaginal microbicide gel containing the antiretroviral drug tenofovir is safe for women to use daily for one week during late-stage pregnancy and while breastfeeding. As the first clinical trial of tenofovir gel conducted among breastfeeding women and only the second among pregnant women, MTN-008 is part of a comprehensive research program established to take incremental steps toward determining whether the gel can safely and effectively protect women against HIV infection during all stages of pregnancy and motherhood. The overall goal of the program is to develop HIV prevention products women can use throughout their lives. MTN-008 was a follow-up study to MTN-002, which found that a single dose of tenofovir gel given to pregnant women hours before giving birth by scheduled Cesarean delivery was safe and well-tolerated by both mother and infant. Based on these reassuring findings, researchers increased the dosage to daily use for one week during both at-term and close-to-term pregnancy in the MTN-008 study. They evaluated the safety of the drug and assessed how much active drug was absorbed during pregnancy and subsequently transferred to the fetus in 91 pregnant women – 45 women at 37 weeks gestation and 46 women at 34 weeks gestation. In 16 breastfeeding mothers, the researchers measured drug levels in breast milk and assessed whether the drug was transferred to the baby.

2. Who conducted and funded MTN-008?
MTN-008was conducted by a team of researchers working with the Microbicide Trials Network (MTN), a clinical trials network established and funded in 2006 by 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). The study, which was funded by NIAID and NICHD, was led by Richard Beigi, M.D., M.Sc., of the University of Pittsburgh School of Medicine and Magee-Womens Hospital.

3. Where and when was the trial conducted?
MTN-008 was conducted at Magee-Womens Hospital of the University of Pittsburgh Medical Center and the University of Alabama, Birmingham (UAB). Participants were enrolled from April 2011 to September 2013.

4. What did the study find?
Results of MTN-008, presented in August 2013 and 2014 and published in July 2016, indicated that daily use of tenofovir gel in the third trimester of pregnancy was safe and well-tolerated. Tenofovir did not accumulate in breast milk of mothers, and absorption of the drug in breastfeeding infants was low – very low levels of the active drug in the gel were transferred to the mothers' milk and breastfeeding infants.

5. What is a microbicide?
Microbicides are products designed to prevent or reduce the sexual transmission of HIV or other sexually transmitted infections when applied inside the vagina or rectum. Most vaginal microbicides are currently being tested as rings, while rectal microbicides are primarily being tested as gels. Microbicides currently being tested contain antiretroviral (ARV) drugs, many of which are commonly used to treat people with HIV.

6. What is tenofovir gel?
In its tablet form, tenofovir is a common treatment for HIV when used in combination with other antiretroviral (ARV) drugs and generally thought to be safe for use by HIV-positive women who are pregnant. Both the

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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.

Clinical studies performed to date have indicated that tenofovir gel is safe and well-tolerated in both HIV-positive and HIV-negative women, although ineffective in preventing HIV due to low adherence to the use of study products, as demonstrated by the VOICE trial, a Phase III study that tested the use of the gel on a daily basis, and FACTS 001, a Phase III study that tested the use of the gel before and after vaginal sex.

7. Why is this study important?
Women represent more than half (51 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. Vaginal microbicides are primarily intended for use by sexually active women of reproductive age, 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.

MTN-008 was only the second study of a vaginal microbicide in pregnancy, and the first in breastfeeding women. It is part of a one-of-a-kind comprehensive research program established at MTN focused on finding products women can safely use to protect against HIV throughout their lives, including pregnancy and motherhood.

8. How was MTN-008 designed?
MTN-008 was a Phase I expanded safety study looking at the daily use of tenofovir gel for one week by 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 gave birth. The study included 107 HIV-negative mother-infant pairs (91 pairs in the pregnancy group and 16 pairs in the nursing group). For the pregnancy group, researchers initially enrolled 45 pregnant women between 37 and 39 weeks gestation and randomized them to receive tenofovir gel or a placebo gel. Women applied their assigned study product (tenofovir gel or placebo gel) daily for seven consecutive days, and underwent evaluation for side effects. Finding no safety concerns, researchers then enrolled a second group of 46 pregnant women who were earlier in their third trimester – between 34 and 36 weeks gestation. As with the first group, these women followed the same seven-day regimen. For the group of breastfeeding women, all 16 participants who were enrolled used tenofovir gel daily for seven days.

9. What tests and procedures did women undergo as part of the study?
The tests and procedures performed during the study included urine and blood tests, vaginal and cervical fluid collection, and pelvic exams and physicals 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. Additionally, in the group of breastfeeding women, the presence of active drug was measured in breast milk and in blood samples from both mother and infant.

10. Is it ethical to test a microbicide in pregnant and nursing women?
Products like tenofovir gel are specifically intended for use by sexually active women – the very women who are most likely to become pregnant. Women need HIV prevention products they can safely use throughout their lives. Researchers can't know whether promising products will be safe and effective to use during pregnancy unless trials are carefully conducted that include pregnant and nursing women. Studies like MTN-008 are designed and implemented with the highest ethical standards and consider the safety and well-being of this special population.

11. Is tenofovir gel safe to give during pregnancy? What about risks to the baby?
MTN-008 researchers took a very careful and step-wise approach to investigating this question in pregnant and breastfeeding women. They would not have conducted MTN-008 without reassuring safety results from earlier studies and MTN-002, which found that a single dose of tenofovir gel given to pregnant women prior to

scheduled Cesarean delivery resulted in only trace amounts of active drug in their bloodstream, and in the amniotic fluid and umbilical cord blood. In MTN-002, the drug levels measured in umbilical cord blood were 40 times lower than drug levels measured in studies of HIV-infected women who took the tablet form of tenofovir while they were pregnant. Researchers of these other studies found very low amounts of tenofovir in the babies of HIV-positive mothers who took the tablet during pregnancy, and neither mothers nor babies had any complications or problems thought to be related to use of the drug. Results of MTN-008 similarly indicated that tenofovir gel was well-tolerated and that very low levels of the active drug in the gel were transferred to the mothers' milk and breastfeeding infants.

12. What was done to ensure the safety of the participants?
MTN-008 was designed according to the most rigorous international medical practice and ethical standards and included numerous measures to monitor and protect the safety and wellbeing of participants, beginning with the clinical research teams at the trial sites who performed thorough checks on the health, safety and welfare of participants at each study visit. In addition, a team at the statistical and data management center (SDMC) assessed incoming reports on a daily basis; three MTN physicians – two specializing in infectious diseases and HIV and the other in obstetrics and gynecology –regularly reviewed summary reports and any concerns raised by site clinicians or the SDMC; and regular reviews were contacted by both a protocol safety review team and a study monitoring committee.

13. Did women participating in the study provide informed consent?
Written informed consent was obtained from all study participants before screening and enrollment. The process ensured that women understood the procedures, as well as possible risks and benefits of the study. Women were under no obligation to participate and were aware they could leave the study at any time, without consequence.

14. What approvals were required to conduct the study?
The study underwent extensive and rigorous review by NIAID, NICHD and the U.S. Food and Drug Administration. The study also was reviewed by the Institutional Review Boards (IRBs) at the University of Pittsburgh and UAB to ensure that it is scientifically valid and ethically conducted. The IRBs at both universities provided oversight throughout the duration of the study.

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More information about MTN-008 and other MTN studies can be found at http://www.mtnstopshiv.org/news.

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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