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## QUESTIONS AND ANSWERS

### **MTN-016: HIV Prevention Agent Pregnancy Exposure Registry**

#### **EMBRACE**

#### **(Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure)**

#### **1. What is the aim of MTN-016, or EMBRACE?**

MTN-016, the HIV Prevention Agent Pregnancy Exposure Registry, is an observational study that seeks to learn whether using different antiretroviral (ARV) products being tested to prevent HIV can affect a woman's pregnancy outcome or her baby's general growth and development. Researchers are conducting the study, also known as EMBRACE (Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure), because women need HIV prevention products that will be safe and effective to use all the time, including when they are pregnant. The study, which began in 2008, involves the creation of a database called a registry containing health information about women who either unintentionally became pregnant while in an HIV prevention trial or who participated in a safety study of vaginal microbicides during pregnancy. In addition, the registry includes information about the health of the babies born to these women. Ongoing and future analyses of registry data will help researchers determine if there are any links between product use and problems that can occur with pregnancy, such as miscarriage, premature delivery or birth defects. Researchers also will be able to evaluate the effects, if any, products may have on an infant's first-year health and growth. To date, the registry includes 420 women and 380 infants.

#### **2. Why is EMBRACE 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 vaginal sex. 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.

Significant strides have been made in ARV-based HIV prevention. However, much less is known about the safety of these products during pregnancy and the effects they may have on pregnancy outcome and infant health. As such, women in HIV prevention trials must use contraception, and if unintended pregnancies occur, they must stop use of study products. In Africa, researchers can expect about 5 to 10 percent of women in a trial to become pregnant during the course of the study. It is also very important to ascertain whether particular products are safe to use during pregnancy before they become widely available. EMBRACE is an important component in a portfolio of MTN studies that are specifically focused on pregnancy, including two trials that have more directly assessed the safety of microbicides in pregnant women.

#### **3. Who is conducting EMBRACE and where?**

EMBRACE is being conducted by a team of researchers who are part of the Microbicide Trials Network (MTN), a clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding by the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all of the U.S. National Institutes of Health (NIH). EMBRACE is being led by Richard Beigi, M.D., M.Sc., of the University of Pittsburgh School of Medicine and Magee-Womens Hospital, and Samuel Kabwigu, MBChB, M.Med., of Makerere University-Johns Hopkins University Research Collaboration in Kampala, Uganda. MTN-016 currently involves 17 trial sites in Malawi, South Africa, Uganda, United States and Zimbabwe.

#### **4. How is EMBRACE different from other HIV prevention studies or registries?**

EMBRACE is not the kind of study that tests different products. But it is an important complement to studies that do. EMBRACE is the first registry for reporting and tracking information about the effects HIV prevention

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products may have on pregnancy outcome and infant health. Unlike most other pregnancy drug exposure registries, EMBRACE also captures information about infant outcomes, including growth during the first year of life. Including this information in the registry data provides a more substantive picture of the potential impact of study product exposure on pregnancy and infant outcomes. EMBRACE is also unique because its design allows researchers to directly compare pregnancy outcomes among women who were exposed to active agents with pregnancy outcomes among women who used a placebo.

### **5. What are the MTN parent studies from which EMBRACE draws its participants?**

EMBRACE draws most of its participants from other MTN trials focusing on evaluation of vaginal microbicides or ARV tablets in the prevention of HIV among women, including:

**VOICE** – Vaginal and Oral Interventions to Control the Epidemic – tested whether ARV medicines commonly used to treat people with HIV are safe and effective in preventing sexual transmission of HIV in women.

VOICE focused on two different ARV-based approaches: daily use of an ARV tablet – an approach called oral pre-exposure prophylaxis, or PrEP – and daily use of a vaginal microbicide containing an ARV in gel form. Specifically, VOICE evaluated the safety and effectiveness of three different products: an oral tablet containing tenofovir (known by the brand name Viread®); an oral tablet that contains both tenofovir and emtricitabine (known as Truvada®); and tenofovir gel, a vaginal microbicide formulation of tenofovir. VOICE was conducted between September 2009 and August 2012 and enrolled 5,029 women in Uganda, South Africa and Zimbabwe. The study’s results, reported in March 2013, found none of the products effective; most participants did not use them daily as recommended.

**ASPIRE** – A Study to Prevent Infection with a Ring for Extended Use – was a Phase III study to determine whether a vaginal ring containing the ARV drug dapivirine is a safe and effective method for protecting against the sexual transmission of HIV when used by women for a month at a time. The study, which was launched in August 2012 and enrolled 2,629 women at 15 sites in Africa, found that dapivirine ring was safe, and reduced the risk of HIV infection by 27 percent overall and by 56 percent in women older than 21. The dapivirine vaginal ring was developed by IPM, which is conducting another Phase III trial, The Ring Study, in parallel with ASPIRE. As sister studies, ASPIRE and The Ring Study were designed to provide the strength of evidence for potential licensure of the dapivirine ring for HIV prevention.

Other women enrolled into EMBRACE were drawn from studies specifically designed to evaluate the safety of microbicides used during pregnancy, including:

**MTN-002** – the first Phase I study of a microbicide ever to be conducted in pregnant women that sought to understand if and to what extent pregnancy affects how the body absorbs the active drug in tenofovir gel and whether the drug could be transferred to the fetus. The gel was applied as a one-time, single dose in 16 healthy HIV-negative women prior to giving birth by scheduled caesarean delivery. MTN-002 found only small amounts of drug are absorbed into the mother’s bloodstream, amniotic fluid and umbilical cord (fetal) blood, that the gel was safe and well-tolerated by both mother and infant.

**MTN-008** – an expanded Phase I study designed to determine whether using tenofovir gel daily for one week is safe for women late in pregnancy and while breastfeeding. As a follow-up to [MTN-002](#), 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 enrolled 90 pregnant women – 45 women at 37 weeks gestation and 45 women at 34 weeks gestation; and 16 women who were breastfeeding. Results indicated that daily use of tenofovir gel in the third trimester of pregnancy was safe and well-tolerated. Tenofovir also did not accumulate in breast milk, and absorption of the drug in breastfeeding infants was low.

### **6. How is EMBRACE being conducted?**

Researchers are collecting and tracking detailed information about a woman’s medical and pregnancy history and the course and outcome of her current (or recent) pregnancy, including details about her delivery. The study also collects baseline information about infants within the first 10 days after delivery and follow-up visits conducted at one, six and 12 months of age. Information gathered at birth and all subsequent visits for an entire year will include comprehensive assessment of growth, general appearance and health – parameters that

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are typically measured in the evaluation of a newborns and infants. Of most interest to researchers is whether a woman had used an active product or a placebo when she became pregnant, or in the case of women in a pregnancy safety study, whether they had been assigned to use an active product or placebo. Because the majority of parent trials are blinded, neither the participants nor the researchers can know which study product a woman had been assigned to use until after that study has been completed and study group assignments have been unblinded.

### **7. How long are women and their infants followed in the registry?**

Pregnant women are followed in the registry until they give birth. Infants are followed during their first year of life, at which time researchers monitor for health risks specific to the HIV prevention products used by their mothers.

### **8. When will information from the registry be available?**

Researchers conduct ongoing analyses as data is collected into the registry. However, because many of the participants in MTN-016 are women who become pregnant during MTN's large effectiveness trials, information about the actual product the women were using – whether it was a product with an active drug or a placebo – can't be entered into the database until after the parent trial has closed and such information has been "unblinded." Registry results for women and infants who participated in MTN-002 and MTN-008 were presented in October 2014, and indicated no differences in pregnancy problems, preterm birth or infant's first-year health among women who received tenofovir gel and those who received a placebo gel. Researchers are currently analyzing data from women in VOICE and ASPIRE who enrolled into MTN-016.

### **9. What ARV drugs have been tested or are currently being tested in MTN trials?**

Women enrolled in the registry may have been exposed to one of several ARV-based products that were tested or are currently being tested in MTN studies, including tenofovir (tablet or gel), Truvada and dapivirine. EMBRACE may eventually also include women from studies that evaluate HIV prevention products containing other active drugs.

Tenofovir and Truvada are approved for the treatment of HIV when used in combination with other ARVs, a regimen called antiretroviral therapy (ART), and have excellent safety profiles and are well tolerated by most HIV-infected people. In addition, Truvada was approved by the U.S. Food and Drug Administration (FDA) in 2012 for HIV prevention. Both drugs belong to a class of anti-HIV medications called nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs) that act against HIV by targeting a key enzyme the virus needs to copy its genetic material – an essential step for the virus to multiply and infect other cells inside the body. Truvada and 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.

Dapivirine, also known as TMC-120, is a type of ARV called a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs bind to and disable HIV's reverse transcriptase enzyme, a protein that HIV needs to make copies of itself. Dapivirine was initially being developed as an oral therapeutic agent to be used in the treatment of HIV, but because of its favorable safety profile and physical and chemical properties it was decided that dapivirine was better suited for development as a microbicide for HIV prevention. As such, it is being developed as a monthly microbicide ring and in other formulations by the International Partnership for Microbicides (IPM) through a royalty-free licensing agreement with Janssen R&D Ireland. Dapivirine vaginal ring was found to be safe and to help prevent HIV in two Phase III studies, MTN's ASPIRE study and IPM's The Ring Study.

### **10. What is known about these ARV drugs and pregnancy?**

Both oral tenofovir and Truvada are designated by the FDA as a pregnancy category B drug, a classification given to drugs in which animal studies have not found fetal risk. Since 1989, researchers have been tracking information about HIV-infected women who may have used these or other ARVs during pregnancy through the Antiretroviral Pregnancy Registry. Each year, the Registry enrolls approximately 1,300 pregnant women in the U.S. exposed to ARVs. To date, registry data indicates no difference in the prevalence of birth defects in pregnant women who took oral tenofovir or Truvada as treatment of their HIV compared to the general population. In other studies, researchers found that while some tenofovir gets transferred to the babies of HIV-

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infected mothers who took the drug during pregnancy, the babies had no complications or problems thought to be drug-related. Less information is known about the use of oral tenofovir and Truvada in pregnant women who are HIV-negative. The Partners PrEP study, which involved couples in which one of the partners had HIV, evaluated both tenofovir and Truvada as HIV prevention. There were 288 pregnancies among the women in Partners PrEP, and researchers found no evidence that any active product was associated with pregnancy complications.

MTN researchers have completed two studies of tenofovir gel in pregnant women who were HIV-negative. In MTN-002, tenofovir gel was applied as a one-time, single dose in healthy HIV-negative women prior to giving birth by scheduled caesarean delivery. Results showed the gel was safe and well-tolerated by both mother and infant, and very small amounts of drug were absorbed into the mother's bloodstream, amniotic fluid and umbilical cord (fetal) blood. In a follow-up study, MTN-008, researchers evaluated how much of the active drug in tenofovir was absorbed in the last trimester of pregnancy and transferred to the fetus. They also measured drug levels in breast milk of breastfeeding mothers and assessed whether the drug was transferred to the baby. Results from MTN-008 indicated that daily use of tenofovir gel in the third trimester of pregnancy was safe and well-tolerated. Tenofovir also did not accumulate in breast milk, and absorption of the drug in breastfeeding infants was low.

Less information is available on the use of dapivirine among pregnant women as it is not an ARV used in the treatment of HIV. To address the need for safety data in this population, MTN researchers are enrolling participants into a Phase I study (MTN-029/IPM 039) to determine whether dapivirine accumulates in the breast milk of lactating women who are using the ring. The study will be a critical first step in understanding whether dapivirine ring would be both safe and effective in women during breastfeeding and pregnancy, when the risk of acquiring HIV from an infected partner is especially high.

### **11. Is contraception provided to women in HIV prevention studies?**

Because the effects of study products on pregnancy are not fully known, women participating in HIV prevention trials must be willing to use effective contraception. The types of contraception offered to participants depends on the contraceptive methods available within the particular country, and what can be offered at the research site and/or at referring clinics.

### **12. What approvals were required for this study to get underway?**

The study underwent extensive and rigorous review by NIAID, NICHD, the U.S. Food and Drug Administration (FDA) and the University of Pittsburgh Institutional Review Board (IRB), as well as local IRBs in the other countries where sites are conducting EMBRACE. IRBs ensure that studies are scientifically valid and ethically conducted by providing oversight throughout the duration of a trial.

### **13. What will be done to ensure the safety and wellbeing of the participants?**

Because EMBRACE is an observational study that does not involve investigational products or risky procedures, few safety concerns have been anticipated. Nevertheless, study investigators are closely monitoring participants. Women are being referred to local services for prenatal and postnatal care. If investigators find medical concerns when examining infants, referrals will be made to local pediatricians for care. The study site staff offers HIV testing for infants, as well as pre-test and post-test counseling for the infants' parents and guardians. Staff at study sites make every effort to protect participants' privacy, but it is still possible that others may learn of a participant's involvement in the study. Study staff offer counseling and other support services to participants as needed.

### **14. Do women and infants participating in the study provide informed consent?**

Women who agree to participate in EMBRACE sign an informed consent form and parents or guardians sign an informed consent form for the infants. The process of obtaining written informed consent ensures that women understand the procedures, as well as possible risks and benefits of the study. Participants are under no obligation to participate and may leave the study at any time, without consequence.

More information about MTN-016 and other MTN studies can be found at <http://www.mtnstopshiv.org/news>.

*About the Microbicide Trials Network*

*The [Microbicide Trials Network](http://www.mtnstopshiv.org) (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](http://www.mtnstopshiv.org).*

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