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BACKGROUND

MTN-016: HIV Prevention Agent Pregnancy Registry

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

Study Overview

MTN-016, the HIV Prevention Against Pregnancy Exposure Registry, is an observational study that seeks to learn whether using a vaginal microbicide or antiretroviral (ARV) tablets – products approved for the prevention and treatment of HIV – can affect a woman’s pregnancy outcome or her baby’s general growth and development. Researchers are conducting MTN-016, also known as EMBRACE (Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure), because women need HIV prevention products that are safe and effective to use all of 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 collected from women who either unintentionally got pregnant while in an HIV prevention trial or who participated in a safety study of 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 development and growth. To date, the registry includes 420 women and 380 infants. EMBRACE is the first registry for reporting and tracking information about the effects that microbicides or ARV tablets as HIV prevention may have on pregnancy outcome and infant health.

EMBRACE is being conducted by the Microbicide Trials Network (MTN), a clinical trials network established and funded in 2006 by the Division of AIDS (DAIDS) 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 National Institutes of Health (NIH). NIAID/DAIDS and NICHD are funding EMBRACE, which is being led by Richard Beigi, M.D., M.Sc., of the University of Pittsburgh School of Medicine, and Samuel Kabwigu, MBChB, M.Med., from the Makerere University in Kampala, Uganda.

Why the Study is Important

Women account for more than half of all HIV infections worldwide, and the majority are acquiring HIV through heterosexual intercourse. In fact, 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. Some studies suggest that during pregnancy, the risk of acquiring HIV from an infected partner during sex may be doubled.

Significant strides have been made in ARV-based HIV prevention, with the U.S. Food and Drug Administration’s approval of Truvada as pre-exposure prophylaxis (PrEP) – a prevention strategy in which people take Truvada® daily to prevent infection – in 2012. Less is known about the safety of some of these products (vaginal microbicides, in particular) during pregnancy and the effects they may have on pregnancy outcome and infant health. As such, women in HIV prevention trials must use contraception, in addition to male condoms, 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. Yet, if a trial would find a particular product effective, and an approach become

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widely available, it is important to know whether that product is safe to use during pregnancy. Indeed, a 2008 Institute of Medicine report on 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 babies. EMBRACE is an important component of a portfolio of MTN studies that are specifically focused on pregnancy, including the first trial assessing the safety of microbicides in pregnant women.

How the Study is Being Conducted

Although women participating in an HIV prevention trial must agree to use contraception, pregnancies are not uncommon. To date, most women enrolled into EMBRACE became unintentionally pregnant while taking part in VOICE – Vaginal and Oral Interventions to Control the Epidemic, a large trial that involved 5,029 women and tested the daily use of a vaginal microbicide containing the ARV tenofovir and daily use of the ARV tablet tenofovir or Truvada, and ASPIRE – A Study to Prevent Infection with a Ring for Extended Use, that tested the monthly use of a vaginal ring containing the ARV drug dapivirine.

Other women who enroll in EMBRACE are drawn from studies specifically designed to evaluate the safety of HIV prevention products directly during pregnancy. EMBRACE is open to women participating in non-MTN HIV prevention trials as well.

Researchers collect and track detailed information about a woman's medical and pregnancy history, the course and outcome of her current (or recent) pregnancy, including details about her labor and delivery. Baseline information about infants within the first 10 days after delivery and developmental screenings conducted at one, six and 12 months of age is also collected. Information gathered at birth and at all visits in the first year includes comprehensive assessment of growth, general appearance and health – parameters that are typically measured in the evaluation of a newborn and infant.

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 each of the parent trials is blinded, neither the participant 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. As such, women enrolled in the registry may have been exposed to an active product or to a placebo – a gel, tablet or ring that looks identical to the active product but contains no active ingredient. Active study products include oral tenofovir, oral Truvada, tenofovir gel or dapivirine, among others.

Tenofovir and Truvada

Tenofovir and Truvada are approved for the treatment of HIV when used in combination with other ARVs, a regimen called antiretroviral therapy (ART). The full name for tenofovir is tenofovir disoproxil fumarate (TDF) and is known by the brand name Viread[®]. Truvada, the brand name for a combination drug that contains tenofovir and another active ingredient called emtricitabine (FTC), was also approved by the FDA in 2012 as pre-exposure prophylaxis (PrEP) – a strategy in which people take it daily to prevent HIV infection. Both tenofovir and Truvada 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. Both drugs have excellent safety profiles and are well tolerated by most people who take them for HIV infection. Both tenofovir and Truvada are designated by the FDA as pregnancy category B drugs, a classification given to drugs in which animal studies have not found fetal risk.

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Since 1989, researchers have been tracking information about HIV-infected women who have used these or other ARVs during pregnancy through the Antiretroviral Pregnancy Registry. Registry data indicates no difference in the prevalence of birth defects from the general population. Similarly, the registry's information on more than 1,300 HIV-infected women annually who received treatment with oral tenofovir during their pregnancies has been no statistically significant differences in birth defects compared to babies whose mothers never took tenofovir. In other studies, researchers found that while some tenofovir gets transferred to the babies of HIV-infected mothers who took the drug during pregnancy, the babies had no complications or problems that were thought to be drug-related.

Less information on the use of tenofovir or Truvada in pregnant HIV-negative women is available, but women taking tenofovir or Truvada who became unintentionally pregnant while participating in the Partners PrEP study, a large clinical trial among heterosexual serodiscordant couples in Kenya and Uganda, had no significant differences in birth complications or their infants' weight and growth compared to women who received a placebo.

Tenofovir Gel

Each dose of tenofovir gel contains approximately 40 mg of active drug. Clinical studies performed to date have indicated that the 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 both the VOICE Study and FACTS 001, a Phase III study that tested the use of the gel before and after sex.

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 also safe and well-tolerated. Tenofovir also did not accumulate in breast milk, and absorption of the drug in breastfeeding infants was low.

Tenofovir, Truvada and tenofovir gel all were developed by Gilead Sciences, Inc., of Foster City, California, USA, which assigned a royalty-free license for the topical gel to International Partnership for Microbicides (IPM) of Silver Spring, Maryland, and CONRAD, in December 2006.

Dapivirine

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 was developed as a monthly microbicide ring and in other formulations by the IPM through a royalty-free licensing agreement with Janssen R&D Ireland. Dapivirine vaginal ring was tested in two Phase III studies, MTN's ASPIRE study and IPM's The Ring Study, and found to be safe and to help prevent HIV.

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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.

Participant Safety

Because EMBRACE is an observational study, few safety concerns have been anticipated. Nevertheless, study investigators closely monitor participants. Women are referred to local services for prenatal care, and if investigators find medical concerns when examining infants, referrals are made to local pediatricians for care. The study site staff also offer HIV testing for infants, as well as pretest and posttest counseling for the infants' parents and guardians.

The study underwent extensive and rigorous review by NIAID, NICHD, the 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 the trial. 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. Staff at study sites make every effort to protect participants' privacy.

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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 <http://www.mtnstopshiv.org>.

15-August-2016