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TRIAL IS FIRST TO SEE IF HIV PREVENTION GELS ARE SAFE FOR PREGNANT WOMEN, THEIR BABIES

Researchers also plan the first registry of women who become pregnant in microbicide trials

PITTSBURGH, June 12, 2008 – Clinical trials hoping to identify a vaginal microbicide that is both safe and effective against HIV have all but skirted questions befitting the evaluation of an approach intended primarily for sexually active women of childbearing age: What if a woman becomes pregnant while using a product? Can exposure to a product, especially early in pregnancy, pose a risk to the developing fetus? Does pregnancy affect how a particular microbicide is supposed to work?

Researchers from the Microbicide Trials Network (MTN) and the University of Pittsburgh will begin addressing these and other questions in the first clinical trial of a candidate vaginal microbicide in pregnant women. The National Institute of Allergy and Infectious Diseases (NIAID) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), both components of the U.S. National Institutes of Health, are funding the study.

Women, who represent nearly half of the 33.2 million people living with HIV, are more than twice as likely as men to acquire HIV through sex. Between 70 and 90 percent of all HIV infections in women are acquired during heterosexual intercourse. In the face of these staggering statistics, much research is focusing on the promise of microbicides, products designed to prevent the sexual transmission of HIV when applied topically on the inside of the vagina or rectum.

The trial, known as MTN-002, will enroll 16 healthy HIV-negative women who are scheduled for caesarean delivery at Magee-Womens Hospital of the University of Pittsburgh Medical Center. The women will have a single dose of tenofovir topical gel applied inside the vagina about two hours before giving birth. Tenofovir gel incorporates an antiretroviral drug normally used to treat people with HIV and is among a newer class of candidate microbicides that differ from early types because it has specific activity against HIV.

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Researchers hope to understand the extent that pregnancy affects how the body absorbs the active drug in the gel and whether the drug can be transferred to the fetus.

"The study of drugs during pregnancy continues to be one of the most neglected areas of biomedical research. As for microbicides, when the very population at risk for HIV is the same population of women most likely to become pregnant, we have a clinical and ethical obligation to pursue studies involving the use and safety of microbicides in pregnancy," said Richard Beigi, M.D., M.Sc., an assistant professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine, who is leading the MTN study.

Women in clinical trials of microbicides are typically between the ages of 18 and 40 and required to use effective methods of contraception, in addition to male condoms, for a study's duration. Still, pregnancies are not uncommon, occurring in at least 5 to 10 percent of participants. Because the risks to both women and their babies are not known, women who are found to be pregnant are told to stop using the study product immediately. "Absent any data, the wisest course of action has been the one we have adopted. But asking women to stop a product is not an approach that would be feasible in a real-world setting, and surely, in the short term, we would do better to have data with which we could inform women in clinical trials," added Dr. Beigi. Dr. Beigi will also lead an MTN registry of women who become pregnant while participating in an HIV prevention trial of either a microbicide or an oral antiretroviral drug, an approach known as pre-exposure prophylaxis, or PrEP; and will include women who have participated in trials like MTN-002. The registry also will help determine the effects, if any, that early exposure to these products may have on fetal and/or neonatal development.

Indeed, 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. One argument for such studies is that if a 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. Moreover, studies could also indicate if using microbicides during pregnancy – a time when women may be at even greater risk for acquiring HIV through sexual intercourse – could also help prevent mother-to-child HIV transmission.

Researchers must first understand what happens in pregnancy, when changes in the mother, placenta and the fetus can alter absorption, distribution and elimination of drugs. In MTN-002, researchers will look to see if and how much of the gel's active drug is in the woman's blood and uterus; the placenta and umbilical cord blood; and the amniotic fluid surrounding the baby. Because study gel is being given as one dose right before delivery, just trace amounts of tenofovir, if any, are expected to pass into the bloodstream. Researchers are not sure if the drug goes into the placenta, the amniotic fluid or the baby's blood, which are some of the questions the study seeks to answer.

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The active ingredient in tenofovir gel belongs to a class of anti-retroviral (ARV) drugs called nucleotide reverse transcriptase inhibitors. In its pill form, tenofovir is a mainstay of one of the most widely used regimens for treating HIV, and it is increasingly being used during pregnancy. It is also being studied in HIV-infected women late in pregnancy for its potential to prevent mother-to-child transmission of HIV. The topical gel form of tenofovir is an approach being evaluated as a preventive against sexual transmission of HIV. Trials have found it is safe to use by HIV-negative women, but no studies of the gel have been conducted in pregnant women. MTN-002 will include several measures to ensure the safety of the women and their newborns, and it will make use of the resources and expertise of the University of Pittsburgh Obstetric-Fetal Pharmacology Research Unit (OPRU), one of four OPRU sites funded by the NICHD to study the use of pharmacologic agents during pregnancy.

Depending on what is learned in MTN-002, the research team may plan larger trials that will assess repeated tenofovir gel use over longer periods during pregnancy. Demonstrating the safety during pregnancy could potentially allow women who become pregnant during effectiveness trials to remain in the study and continue using the product, say the researchers.

Concurrent with MTN-002, MTN will launch a series of other trials evaluating the safety of and adherence to using tenofovir gel as well as looking at its effectiveness for preventing HIV in nonpregnant women. MTN-001will be the first study directly comparing oral and vaginal gel preparations of tenofovir – looking at differences in drug absorption (systemically and locally) and adherence and acceptability of each approach separately and in combination. The VOICE Study (Vaginal and Oral Interventions to Control the Epidemic) will be the first effectiveness trial evaluating two promising HIV prevention approaches in the same study: tenofovir gel and PrEP, an HIV prevention approach that involves daily use of oral ARVs.

Both oral and topical formulations of tenofovir were developed by Gilead Sciences, Inc., of Foster City, California, 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. CONRAD is supplying both the gel and gel applicators for MTN-002.

Other microbicide products have been or are currently being tested in clinical trials, although none is yet approved or available for use by women.

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

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH). The MTN brings together international investigators, community and industry partners who are devoted to reducing the sexual transmission of HIV through the development and evaluation of microbicides, working within a unique infrastructure specifically designed to facilitate research required to support licensure of topical microbicide products for widespread use. Based at the University of Pittsburgh and Magee-Womens Research Institute, MTN's principal investigator is Sharon Hillier, Ph.D. MTN's core operations are supported by a network laboratory at the University of Pittsburgh, a statistical and data management center housed within the Statistical Center for HIV/AIDS Research & Prevention at the Fred Hutchinson Cancer Research Center, and Family Health International, a global organization with expertise conducting clinical protocols. It receives its funding from three NIH institutes: NIAID, the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.