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Researchers report results of first microbicide trial in pregnant women
Study indicates small amount of drug passes to fetus

PITTSBURGH, May 23, 2010 – Results of the first trial of a vaginal microbicide in pregnant women are bringing the field a step closer to answering a critical question–whether microbicides, products that are being developed for women to protect themselves against HIV, are safe for women and their babies if used during pregnancy.

The study, which involved giving a single dose of the antiretroviral (ARV)-based microbicide tenofovir gel to healthy, HIV-uninfected women hours before they gave birth, was conducted to determine how the drug is absorbed during pregnancy and whether it can transfer to the fetus. Only small amounts of drug were absorbed into the mother's bloodstream, amniotic fluid and umbilical cord (fetal) blood after topical application of the gel, reported Richard Beigi, M.D, MSc., who led the National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN) study known as MTN-002. The results were presented at the International Microbicides Conference in Pittsburgh.

In tablet form, tenofovir is an ARV approved for the treatment of HIV as part of standard therapy, and both research and clinical experience with the oral drug have indicated its use is safe in HIV-infected women during pregnancy. The oral drug is also being studied for prevention of mother-to-child transmission of HIV. The researchers conducting the current study of tenofovir gel found that after a 40-mg single dose of the gel, the amount of drug in umbilical cord blood was 40 times lower than what was seen in the studies in HIV-infected women receiving a single 600 mg dose of oral tenofovir. The median drug levels found in maternal blood were 50 to 100 times lower with the tenofovir gel than with oral dosing.

"If a microbicide is found effective for preventing HIV in women, women will need to know whether it is safe for use during pregnancy, and would not be harmful to their unborn child. We are committed to understanding the answers to these questions, but we must do so in step-wise fashion, with the greatest of care and in the most ethically responsible way possible," said Dr. Beigi, who is an assistant professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine.

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"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," he added.

Microbicides are substances intended to reduce or prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside the vagina or rectum. They are being developed because 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 several studies suggest the risk of acquiring HIV doubles. Because no information has been available to know whether using a candidate microbicide during pregnancy is safe, women who participate in clinical trials must use contraception, and if women become pregnant, they must stop using study product– at a time when protection against HIV may be needed the most.

MTN-002 was a Phase I trial in which a single dose (40 mg) of tenofovir gel was applied in 16 healthy HIV-negative women approximately two hours before they gave birth by scheduled caesarean delivery. Researchers took maternal blood samples before and up to 24 hours after the gel was applied and collected samples of the amniotic fluid surrounding the baby, umbilical cord blood, placental tissue and uterine tissue. 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.

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 level detected in the amniotic fluid was also small and it was less than what had 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 , called MTN-008, that will involve both pregnant and breastfeeding women.

These studies come at an important time. 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 in pregnant women demonstrating safety could potentially allow women who become pregnant during effectiveness trials to continue using the product.

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Moreover, if tenofovir gel or any other microbicide were to become widely available, pregnant women likely 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. Indeed, a recent Institute of Medicine report on the 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 fetuses.

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. The study 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 NIH. MTN-002 was funded by the Division of AIDS, NIAID; and NICHD. CONRAD of Arlington, Virginia, provided both the gel and the applicators.

In addition to Dr. Beigi, other authors of the study presented at M2010 are: Lisa Noguchi, CNM, MSN; and Ratiya P. Kunjara, MT ASCP, both of MTN and Magee-Womens Research Institute; Ingrid Macio,PA-C, Magee-Womens Hospital of UPMC; Craig Hendrix, M.D., Johns Hopkins University School of Medicine; Benoît Mâsse, Ph.D., Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Megan Valentine, PA-C, MS, Family Health International; D. Heather Watts, M.D., NICHD; and Jeanna M. Piper, M.D., Division of AIDS, NIAID.

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

About the Microbicide Trials Network

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 who are devoted to preventing or reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.