First combination ARV vaginal ring for HIV prevention being tested in Phase I safety trial

November 15 2011

In the first clinical trial of a vaginal ring combining two antiretroviral (ARV) drugs, researchers from the Microbicide Trials Network (MTN) are collaborating with the International Partnership for Microbicides (IPM) to evaluate whether the ring is safe for use in women. If the ring does prove to be safe, it could be considered for further testing, and eventually be evaluated for its effectiveness as a microbicide for protecting women against HIV infection through vaginal sex.

The trial, which is funded by U.S. National Institutes of Health and goes by the name MTN-013/IPM 026, is evaluating a ring that contains the ARVs dapivirine and maraviroc. Each of these drugs works against HIV in a different way. Dapivirine belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTIs) that prevent HIV from making copies of itself. Maraviroc, on the other hand, is an entry inhibitor that blocks HIV from getting inside target cells.

The dapivirine-maraviroc ring is the first combination microbicide to enter clinical trials. It is also the first vaginal microbicide containing an entry inhibitor.

The ring was developed by IPM, a non-profit product development partnership headquartered in Silver Spring, Maryland, in collaboration with Queens University Belfast (Belfast, Northern Ireland). The belief is that combining the two drugs, which act at different points in the HIV "life cycle," may provide greater protection against HIV than a single drug alone.

Globally, women comprise half of the 34 million people living with HIV. In sub-Saharan Africa, women represent nearly 60 percent of adults with the virus. In most cases women – especially young women – acquire HIV through unprotected heterosexual sex with an infected partner. Because the use of condoms is often not an option, there is an urgent need for effective prevention strategies that women can control themselves. Toward this end, vaginal microbicides in the form of a gel or a ring, for example, are being developed to provide women with new tools to protect themselves against HIV.

Vaginal rings provide slow, continuous delivery of a drug or multiple drugs to cells inside the vagina over a period of weeks or months. Marketed vaginal ring products include those used for contraceptive delivery and hormone replacement. However, vaginal rings can also be used as a vehicle for delivering potent ARV drugs into the vagina to prevent HIV infection. Because they could be used for one month at a time, vaginal rings may offer a long-acting and convenient prevention option for women.

MTN-013/IPM 026, which is now screening potential participants, will enroll 48 healthy, HIV-negative women ages 18-40 at the University of Pittsburgh, Fenway Institute in Boston and the University of Alabama at Birmingham. Researchers will evaluate the ring's safety and how well women like or are willing to use the ring. In addition, different tests will be performed to help determine how much of each drug is taken up by the cells usually targeted by HIV and whether drug levels are sustained throughout the four weeks the ring is worn.

Women will be randomly assigned to use either the combination dapivirine-maraviroc ring, a ring containing maraviroc alone, a ring that contains dapivirine alone, or one with no active drug. This will enable researchers to compare the safety and drug delivery capability of the combination ring with each single-drug ring and with the placebo ring.

All the rings in the study look the same. They are made of silicone elastomer and measure 56 mm (about 2 ¼") in diameter and 7.7 mm (¼") thick. Women will wear their assigned ring for 28 days. Different tests and procedures will be conducted during this time as well as during a 24-day follow-up period.

Leading the study for the MTN is Beatrice A. Chen, M.D., M.P.H., of the University of Pittsburgh School of Medicine and Magee-Womens Hospital of UPMC, who is protocol chair; with Lori Panther, M.D., M.P.H., of the Fenway Institute and Harvard University in Boston, as protocol co-chair.

"IPM has been a pioneer in developing vaginal rings for delivery of antiretrovirals. Our collaboration marks an important juncture for the field as we begin to explore drugs with different mechanisms of action and methods that we hope will give women new, easy-to-use options for preventing HIV," remarked MTN Principal Investigator Sharon Hillier, Ph.D., who is professor and vice chair for faculty affairs, and director of reproductive infectious disease research in the department of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine.

"Our partnership with MTN on the first combination microbicide to enter clinical trials is an important milestone for the HIV prevention field," said Zeda F.Rosenberg, Sc.D., IPM chief executive officer. "With extensive preclinical data on both drugs to support the combination ring's development, we hope this product will one day expand women's HIV prevention options and open the door to developing other combination HIV prevention methods."

IPM holds royalty-free licenses to develop both maraviroc and dapivirine as vaginal microbicides for the prevention of HIV in developing countries. IPM's primary focus has been the development of

ARVs as microbicides in a variety of dosage forms.

Dapivirine – a drug developed by Tibotec Pharmaceuticals, one of the Janssen pharmaceutical companies– was tested initially as an oral treatment for HIV. In 2004, Tibotec provided IPM with a license to develop the drug as a vaginal microbicide for HIV prevention. Since then, 15 clinical safety studies of dapivirine, formulated as either a vaginal gel or a vaginal ring, have been conducted by IPM and its partners showing that it is safe and well-tolerated by women. MTN recently completed a male tolerance study of dapivirine gel. Results are expected in the first half of next year.

Next year, the MTN will launch a Phase III effectiveness trial of the dapivirine-only ring. The study, called ASPIRE – A Study to Prevent Infection with a Ring for Extended Use – will enroll approximately 3,475 women at sites in five African countries.

As part of IPM's strategy to license the dapivirine ring, IPM will conduct The Ring Study (IPM 027), which will be done in parallel with ASPIRE, and collect long-term safety and efficacy data about the ring among approximately 1,650 women at multiple research centers in Africa.

IPM is developing maraviroc as a microbicide through a 2008 licensing agreement now held by ViiV Healthcare. Maraviroc is approved for use in the treatment of HIV in combination with other ARVs and is marketed under the trade names Selzentry® in the United States and Celsentri® in Europe. Because maraviroc is not widely used in Africa and is the only drug of its class, it is likely to remain active against HIV strains that have become resistant to other classes of ARVs used more widely to treat HIV. Therefore, it is a very promising candidate for HIV prevention. IPM has completed several preclinical studies of maraviroc, and is exploring its development as a microbicide both alone and in combination with dapivirine or tenofovir. The MTN-013/IPM 026 study

will be the first time that maraviroc will be evaluated as a microbicide in humans.

MTN-013/IPM 026 is expected to take less than a year to complete with results available early 2013. It is being funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Mental Health (NIMH), components of the U.S. National Institutes of Health (NIH). IPM will provide the active and placebo rings that will be tested in the Phase I trial.

More information: Additional information about MTN-013/IPM 026 is available at www.mtnstopshiv.org/news/studies/mtn013/qa Information about other MTN studies can be found at www.mtnstopshiv.org/news/studies

Provided by Microbicide Trials Network