

Combination ARV vaginal ring to prevent HIV safe in trial but one ARV carries the weight

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An early phase clinical trial of a vaginal ring containing the antiretroviral (ARV) drugs dapivirine and maraviroc found the ring was safe in women who wore it for 28 days and evidence of dapivirine in cervical tissue and blood. In addition, laboratory tests of tissue samples showed that dapivirine was able to block HIV infection, though levels of maraviroc were not sufficient to have a similar effect, reported researchers from the National Institutes of Health-funded Microbicide Trials Network (MTN) today at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

The Phase I trial, known as MTN-013/IPM 026, was the first clinical study of a vaginal microbicide with two ARV drugs, and with the inclusion of maraviroc, the first involving an ARV belonging to a class of anti-HIV drugs called entry inhibitors. Microbicides are products applied inside the vagina or rectum to prevent the sexual transmission of HIV. Vaginal microbicides are being designed in many forms, including gels, films and rings that, once inserted into the vagina, release the active ingredient gradually over time.

"It's encouraging that both drugs were safe, and that most [women](#) didn't mind wearing the ring. However, we found maraviroc wasn't getting absorbed in tissue like dapivirine was and it didn't work as well as dapivirine in our laboratory studies looking at activity against HIV," explained Beatrice A. Chen, M.D., M.P.H., of the University of

Pittsburgh School of Medicine and Magee-Womens Hospital of UPMC, who as protocol chair of MTN-013/IPM 026, presented the results on behalf of the study team.

Though the findings indicate that further work is needed on the development of the combination ring, they bode well for the dapivirine ring, which is currently being evaluated in two ongoing Phase III effectiveness trials in Africa: the ASPIRE trial led by MTN and The Ring Study led by the nonprofit International Partnership for Microbicides (IPM). IPM developed both the dapivirine ring and the combination dapivirine-maraviroc ring.

MTN-013/IPM 026 was designed to evaluate the safety, acceptability and drug absorption qualities of the dapivirine-maraviroc ring when worn by women for 28 days. It enrolled 48 HIV-negative women ages 18 to 40 at the University of Pittsburgh, The Fenway Institute in Boston, and the University of Alabama at Birmingham (UAB) and was conducted between September 2011 and September 2012. Women were randomly assigned to use either the combination dapivirine-maraviroc ring, a ring containing maraviroc alone, a ring containing dapivirine alone, or one with no active product. The rings are made of a silicone elastomer, each measuring 56mm (about 2 ¼ inches) in diameter and 7.7mm thick (¼inch).

Of the few side effects experienced by women, most were considered mild in nature and not thought to be associated with use of the ring. Women also found the ring generally acceptable, although 17 percent of the women said they preferred not wearing the ring during menstruation. Of the 48 women in the trial, 45 of them kept the ring in place at all times throughout the 28 days.

"The vast majority of women said they had no discomfort wearing the ring, though some had some concerns about this. Most women said they

forgot it was in place," said Lori Panther, M.D., M.P.H., of The Fenway Institute and Harvard University, who is the MTN-013/IPM 026 protocol co-chair. "The rings are quite similar to the [vaginal ring](#) currently approved for contraception."

Researchers collected samples of blood, vaginal fluid and cervical tissue at different time points during the four weeks that women wore the ring, as well as after it was removed, in order to assess how much of each drug was being absorbed. Dapivirine was detected in all three types of samples. Laboratory tests of cervical tissue biopsies from women using either the dapivirine-only ring or the combination dapivirine-maraviroc ring also showed that dapivirine protected the tissue against HIV infection. In addition, researchers noted a direct correlation between drug concentration levels and protection against HIV for both rings containing dapivirine in the lab tests.

Biopsies from women using the maraviroc-only ring did not show protection against HIV in the laboratory model and maraviroc was not detected in blood. Only 4 of 24 women using either the combination ring or the maraviroc-only ring had detectable levels of the drug in cervical tissue. Additional testing of blood is ongoing to determine whether the drug can be detected using more sensitive methods.

"As an entry inhibitor, maraviroc is a promising candidate for development as a microbicide for HIV prevention because it acts at a different step in the infectious process from other HIV prevention drugs" said Zeda F. Rosenberg, Sc.D., chief executive officer of IPM, a nonprofit organization developing HIV prevention tools and other sexual and reproductive health technologies for women. "IPM is conducting additional development work to increase the amount of maraviroc that gets into cervical tissue in order to best harness the drug's potential in the combination ring, and we are planning a second safety study for 2015."

IPM is developing maraviroc as a microbicide through a royalty-free licensing agreement with 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. Dapivirine, also known as TMC-120, is being developed as a monthly microbicide ring and in other formulations by IPM through a royalty-free licensing agreement with Janssen R&D Ireland.

The two drugs work against HIV in different ways. As an entry inhibitor, maraviroc is designed to block HIV from getting inside target cells, while dapivirine belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTIs) that prevent HIV from making copies of itself. Prior to MTN-013/IPM 026, clinical trials of ARV-based microbicides were only of products containing an NNRTI or nucleoside reverse transcriptase inhibitors (NRTIs). Tenofovir, for example, is an NRTI being tested in both vaginal and rectal microbicide gel formulations.

Provided by Microbicide Trials Network

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