Two studies advance HIV prevention options for women

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Two early clinical studies of novel HIV prevention products for women—the first combination antiretroviral (ARV) vaginal ring and a vaginal film—show the products to be safe and open the door to product improvements that could expand options for women-initiated prevention tools. The results of both studies were presented today at the 21st Conference on Retroviruses and Opportunistic Infections (CROI).

The combination ring study, known as MTN-013/IPM 026, was conducted by the National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN), in collaboration with the International Partnership for Microbicides (IPM), which developed the product. The study evaluated the safety of IPM's vaginal ring designed to provide sustained release of the ARV drugs dapivirine and maraviroc for one month.

The vaginal film study, known as FAME-02 (Film Antiretroviral Microbicide Evaluation), evaluated a film releasing the ARV dapivirine for use around the time of sex. Researchers at the University of Pittsburgh and Magee-Womens Research Institute (MWRI) in Pittsburgh conducted the study, which was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), a component of the NIH. IPM provided dapivirine to MWRI, which then developed the film. The study compared the film to dapivirine gel, which IPM developed and evaluated previously in Phase II trials.

"Women bear an unequal burden of the HIV/AIDS epidemic, and these

two products bring new hope to the fight against HIV," said Dr. Zeda F. Rosenberg, ScD, chief executive officer of IPM. "IPM remains committed to working with partners to ensure that women around the world have an array of options to protect themselves, and these early results will lead the way to the next steps in development on two new approaches."

Combination Ring Study Results (MTN-013/IPM 026)

MTN-013/IPM 026 was the first clinical study of a vaginal ring to combine two ARVs and the first vaginal microbicide in development that contains maraviroc.

The two drugs in the slow-release combination ring work against HIV in different ways. Dapivirine belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTIs) that prevent HIV from making copies of itself. Maraviroc, an entry inhibitor, blocks HIV from getting inside target cells. 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, particularly in the presence of drug-resistant HIV virus.

The monthly combination ring was found to be safe and well-tolerated, and acceptable by the 48 participants enrolled in the MTN-led study. The Phase I clinical study took place at the University of Pittsburgh, the Fenway Institute in Boston and the University of Alabama at Birmingham. Women were randomly assigned to use the combination dapivirine-maraviroc ring, a ring containing only maraviroc, a ring containing only dapivirine or one with no active drug. The study's protocol chair, Beatrice A. Chen, MD, assistant professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine, reported the results.

Study researchers detected dapivirine in blood, vaginal fluids and cervical tissue. Blood levels of dapivirine were low, consistent with previous studies showing dapivirine's low systemic absorption when delivered as a microbicide.

Dapivirine levels in vaginal fluids and cervical tissue—where the drug would be needed locally to prevent infection—were high. In addition, cervical tissue biopsied from women assigned to use the dapivirine-only ring and combination dapivirine-maraviroc ring showed protection against HIV when "challenged" with the virus in laboratory tests. These results further support IPM's dapivirine-only ring, now in two parallel Phase III studies in Africa.

Although maraviroc could be detected in the vaginal fluid of the women in the study, few women had maraviroc detected in the tissue. Thus, it was not surprising that the cervical tissue of women assigned to the maraviroc-only ring was not protected against infection when challenged with HIV ex vivo. It is possible that an increased dose of maraviroc or a different version of the ring will be needed to increase the amount of the drug absorbed into cervical tissue and better harness maraviroc's potential. The optimized combination ring is being developed by IPM and will be ready for clinical testing in 2015.

"MTN looks forward to continuing our collaboration with IPM on the optimized combination dapivirine-maraviroc ring," said Sharon Hillier, PhD, MTN's principal investigator, 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. "Combination ARV products could be the future of HIV prevention given their potential to prevent infection with future drug-resistant HIV and help ensure efficacy over time. Today's results are crucial first steps in pursuing research in that direction for women everywhere."

IPM is developing maraviroc as a microbicide alone and in combination with other ARVs 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. 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.

IPM is developing dapivirine as a microbicide ring and in other formulations through a royalty-free licensing agreement with Janssen R&D Ireland.

Vaginal Film Study Results (FAME-02)

Vaginal films are a novel dosage form for delivery of drugs to the vagina. Films may have advantages over gels including low volume, which translates to less vaginal discharge with use compared to a gel, in addition to lower production costs.

The FAME-02 Phase I study, the first human study to evaluate a vaginal film containing an ARV drug, compared the safety, drug absorption and drug distribution of dapivirine film to dapivirine gel. Sixty women were assigned to use the dapivirine film, placebo film, dapivirine gel or placebo gel for seven days. Drug levels in blood and tissue were measured within two hours after the last dose. Biopsied tissues obtained from the women two hours after the last use of the product were exposed to HIV in the laboratory to assess whether the drug present was adequate to block infections in the female genital tract tissues.

The levels of dapivirine in the blood were comparable across the film and gel arms, suggesting that both products can deliver drugs in a similar manner. While the levels of dapivirine in vaginal tissue were higher in

gel users than film, both the film and gel protected against HIV in challenge models of biopsied cervical tissue.

The study's results were presented at CROI by Katherine Bunge, MD, assistant professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine.

"The results of the FAME-02 study signal early promise for developing a new and convenient product women could use to prevent HIV-1," said Bríd Devlin, PhD, executive vice president of product development at IPM. "The dapivirine film could one day add a very affordable, discreet and convenient option to the method mix for women."

"Quick dissolving films are commercially available for a range of products from breath fresheners to supplements," Dr. Bunge added. "This study has shown that this same technology can deliver ARV drugs for the prevention of HIV. We are quite excited about the potential application of this technology to make more prevention options available for women everywhere."

HIV/AIDS is among the greatest obstacle to women's health and development. In some parts of sub-Saharan Africa, women ages 15-24 are three to four times more likely to be infected with HIV as men in the same age group. Women-initiated tools in the form of rings, films and gels are being developed because our best weapon against HIV will be a range of unique options that give women control over their own protection.

Provided by International Partnership for Microbicides (IPM)