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QUESTIONS AND ANSWERS

MTN-013/IPM 026:

Phase I Safety and Drug Absorption Trial of a Combination Dapivirine-Maraviroc Vaginal Ring

1. What was the aim of MTN-013/IPM 026?
MTN-013/IPM 026 was a Phase I study that aimed to evaluate the safety, acceptability and drug absorption qualities of a vaginal ring being developed as a possible method for protecting women against HIV infection through vaginal sex. Vaginal rings are products designed to allow for the slow delivery of a drug or multiple drugs to cells inside the vagina over a period of weeks or months. MTN-013/IPM 026 was the first clinical trial of a vaginal ring containing two antiretroviral (ARV) drugs: dapivirine and maraviroc. Before researchers can conduct a trial to determine whether the dapivirine-maraviroc ring is effective in *preventing* HIV, they first must know that it is safe and acceptable for women to use. In addition, it is important to know 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 that the ring is worn.

2. Who conducted and funded the study?
MTN-013/IPM 026 was a study of the Microbicide Trials Network (MTN), an HIV/AIDS clinical trials network funded by the National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health (NIMH), all components of the U.S. National Institutes of Health (NIH). NIAID and NIMH are the main sponsors of the study. As co-sponsor and the developer of the rings that were tested in the trial, the International Partnership for Microbicides (IPM), a non-profit product development partnership based in Silver Spring, Maryland, provided the study products for free. As protocol chair, Beatrice A. Chen, M.D., M.P.H., of the University of Pittsburgh School of Medicine and Magee-Womens Hospital of UPMC, led the study, with Lori Panther, M.D., M.P.H., of The Fenway Institute and Harvard University in Boston, as protocol co-chair.

3. When and where was MTN-013/IPM 026 conducted?
MTN-013/IPM 026 was conducted at three NIAID-funded clinical research sites affiliated with the MTN: the University of Pittsburgh, The Fenway Institute and the University of Alabama at Birmingham. The study was conducted between September 2011 and September 2012. Results were presented at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in March 2014.

4. What was unique about MTN-013/IPM 026?
In testing a vaginal ring containing maraviroc, MTN-013/ IPM 026 was the first clinical trial of a vaginal microbicide based on a type of ARV called an entry inhibitor. Entry inhibitors block HIV from being able to enter human cells. To date, all other clinical trials of ARV-based microbicides have focused on ARVs called nucleoside or non-nucleoside reverse transcriptase inhibitors (NRTIs or NNRTIs).These include tenofovir (an NRTI) formulated as a vaginal and rectal gel and dapivirine (an NNRTI) formulated as a vaginal gel and a ring. MTN-013/ IPM 026 was also the first clinical study of a vaginal microbicide containing two active drugs. A ring with two drugs, each having a different mechanism of action against HIV, potentially may be more effective in defending against HIV than a ring with a single drug.

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5. What rings were studied in MTN-013/IPM 026?
Researchers tested three vaginal rings in MTN-013/IPM 026: a ring that contains 25mg of the ARV dapivirine; a ring that contains 100mg of the ARV maraviroc; and a ring containing both a 25-mg dose of dapivirine and a 100-mg dose of maraviroc. A fourth ring, a placebo, contained no active drug. The rings are made of a silicone elastomer, each measuring 56mm (about 2 ¼ inches) in diameter and 7.7mm thick (¼inch).

Dapivirine ring
Dapivirine, also known as TMC-120, is a type of ARV that binds to and disables HIV's reverse transcriptase enzyme, a protein that HIV needs to make copies of itself. Dapivirine was initially being developed as an oral therapeutic agent to be used in the treatment of HIV, but because of its favorable safety profile and physical and chemical properties it was decided that dapivirine was better suited for development as a microbicide for HIV prevention. Dapivirine 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. Since 2004, 16 clinical safety studies of dapivirine, formulated as either a vaginal gel or a vaginal ring, have been conducted by IPM and its partners, including the MTN. Studies of the dapivirine ring show that it can deliver high concentrations of active drug to vaginal tissue for a month or longer, with only trace amounts of the drug being absorbed elsewhere in the body. Furthermore, studies to date have found that use of the dapivirine ring is safe and well-tolerated by women, and that among women in Africa, the vaginal ring itself is highly acceptable as a potential method for HIV prevention. The dapivirine ring is being evaluated in two ongoing Phase III effectiveness trials in Africa: the ASPIRE trial led by MTN and The Ring Study being led by IPM.


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Maraviroc ring
Maraviroc is an ARV marketed under the trade names Selzentry® in the United States and Celsentri® in Europe for use in combination with other oral ARVs for treating people infected with HIV. It works by blocking a molecule, called a receptor, on the surface of cells that the most common strains of HIV use for gaining entry. IPM is developing maraviroc as a microbicide through a royalty-free licensing agreement with ViiV Healthcare. Because maraviroc is licensed as an oral drug, there is extensive preclinical and clinical safety information as well as data on its efficacy since being approved for treatment of HIV in 2007. IPM considers maraviroc a highly promising compound because it is active against HIV strains that are resistant to other ARVs. IPM has completed several preclinical studies of maraviroc and is exploring its development as a microbicide formulated as a vaginal ring both alone and in combination with dapivirine or tenofovir. The MTN-013/IPM 026 study was the first time that a maraviroc-based microbicide was evaluated in humans.

Combination dapivirine-maraviroc ring
IPM has conducted extensive preclinical studies of a dapivirine-maraviroc vaginal ring, that combined with the large portfolio and clinical experience using maraviroc in the treatment setting and the encouraging research on the dapivirine ring to date, supported its further evaluation in a Phase I clinical study.

6. How was MTN-013/IPM 026 designed?
MTN-013/IPM 026 was a Phase I study that enrolled 48 HIV-negative women between the ages of 18 and 40 who agreed to use contraception and remain sexually abstinent throughout their participation in the trial. Participants were randomized to use one of four rings: a combination dapivirine-maraviroc ring, dapivirine-only ring, maraviroc-only ring, or a placebo ring with no active drug. Women inserted the ring themselves (or with the assistance of a clinician) on the day they enrolled and were to remove it after 28 days of use.

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. Each study visit included a physical exam, and pelvic exams were performed at other intervals during the study when small tissue samples of the cervix were also taken. Similar tests and procedures were conducted during a 24-day follow-up period after the ring was removed.

To assess women's adherence to and acceptability of the ring, participants were asked questions about what they liked or didn't like about the ring, whether it was easy to insert and remove, whether they were aware of the ring or found it comfortable during daily activities and about their willingness to use a vaginal ring in the future, if one were available, to protect against HIV infection.

7. What were the results of MTN-013/ IPM 026?

MTN-013/IPM 026 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. 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 found the ring generally acceptable, although 17 percent of the women said they preferred not wearing the ring during menstruation. The vast majority of women said they had no discomfort wearing the ring, and most women said they forgot it was in place Of the 48 women in the trial, 45 of them kept the ring in place at all times throughout the 28 days.

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.

8. Why was this study important?

Of the more than 35 million people living with HIV, more than half (52 percent) are women, who account for nearly 60 percent of those with HIV in sub-Saharan Africa. The majority of women acquire HIV through unprotected heterosexual intercourse with an infected partner. In fact, 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. Young women are especially vulnerable. In southern Africa, young women are up to five times more likely to become infected with HIV than young men. Efforts to promote abstinence, monogamy and the use of condoms have not been enough to stop the HIV epidemic nor are these methods practical in most settings. There is an urgent need for effective prevention strategies that women can control themselves. Toward this end, vaginal microbicides are HIV prevention products being developed especially for use by women to help reduce their risk of HIV infection through vaginal sex.

To date, clinical trials have primarily focused on microbicides formulated as vaginal gels, with a gel based on the ARV tenofovir showing particular promise. Tenofovir gel is being tested for its efficacy when used daily and in a regimen used before and after sex. But for some women, a microbicide in the form of a vaginal ring, which can be used monthly, may be more suited to their particular needs or lifestyles, and therefore, more likely to be used. A product only has a chance of being effective if it is used and used properly. Of the vaginal rings being developed for HIV prevention, the dapivirine ring is the farthest along. Two Phase III studies — The Ring Study and ASPIRE — are now being conducted across 20 sites in Africa to determine whether the ring prevents HIV infection in women and is safe when worn for a month at a time. MTN-013/ IPM 026 represents an important step toward the development of a safe and effective product that employs a drug that works differently than either dapivirine or tenofovir. Moreover, the study is important for determining whether a combination ring can be considered for further study in larger clinical trials.

9. What is the difference between a vaginal microbicide and a vaginal ring?

Microbicides are products designed to prevent or prevent the sexual transmission of HIV when applied inside the vagina or rectum. A microbicide can be formulated in many ways, such as a vaginal or rectal gel, or as a vaginal ring that once inserted releases the active ingredient gradually over time. Vaginal rings that are being developed for HIV prevention are seen as alternatives to microbicides formulated as a gel, which would be

used every day or at the time of sex. Different microbicide products are being tested in clinical trials, including in trials being conducted by the MTN, although none is currently approved or available for general use. The rings that are being developed for HIV prevention have a similar look and feel to vaginal ring products that are used for contraceptive delivery or hormone replacement and licensed in both the U.S. and Europe.

10. What was done to ensure the safety of participants in MTN-013/IPM 026?
MTN-013/IPM 026 was designed according to the most rigorous international medical practice and ethical standards and included numerous measures, beginning at the site level, intended to protect the safety and well-being of participants. Potential volunteers were carefully screened by study staff to ensure that only women for whom it would be safe to participate were enrolled. Site staff provided continuous close safety monitoring of all study participants. As with all NIH-funded studies, MTN-013/IPM 026 incorporated a multi-tiered safety review process that included strict national and international standards and procedures for monitoring and reporting. Prior to implementation, the protocol underwent extensive and rigorous review by NIAID, the U.S. Food and Drug Administration and the institutional review boards (IRBs) at each trial site. IRBs ensure that studies are scientifically valid and ethically conducted and they provide oversight throughout the duration of a trial.

Because this was the first study of the maraviroc ring and dapivirine-maraviroc ring, participants were strongly urged to remain sexually abstinent during the study.

11. Did women participating in the study provide informed consent?
Yes. Women who volunteered to join MTN-013/IPM 026 were educated about all the study procedures, any possible risks, benefits and alternatives to participation as well as the study's time requirements. Study staff also explained that women did not have to take part in the study and could leave it at any time, without consequence. This process is called "informed consent" and it occurred prior to screening, again at enrollment, and continued throughout the duration of the study.

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More information about MTN-013/IPM 026 can be found at http://www.mtnstopshiv.org/news/studies/mtn013. Information about ASPIRE and the Ring Study of the dapivirine vaginal ring is available at: http://www.mtnstopshiv.org/news/studies/mtn020

About the MTN

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 whose work is focused on the development and rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org.

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