SUMMARY

- ASPIRE – A Study to Prevent Infection with a Ring for Extended Use, also known as MTN-020, is a Phase III study that seeks to determine whether a vaginal ring containing the antiretroviral (ARV) drug dapivirine is a safe and effective method for protecting against the sexual transmission of HIV when used by women for a month at a time. The study, which was launched in August 2012, will enroll up to 3,476 women at 15 clinical research sites in Africa and take approximately two years to conduct, with results anticipated late 2014 or early 2015.

- ASPIRE is a study of the Microbicide Trials Network (MTN) and is funded by the National Institute of Allergy and Infectious Diseases and the National Institute of Mental Health, which are part of the U.S. National Institutes of Health (NIH). Jared Baeten, M.D., Ph.D., of the University of Washington, U.S., is protocol chair; and Thesla Palanee, Ph.D., of the Wits Reproductive Health and HIV Institute, South Africa, is protocol co-chair.

- The dapivirine ring was developed by the International Partnership for Microbicides (IPM), which is also the regulatory sponsor and license holder of the product. IPM is conducting another effectiveness trial of the dapivirine ring called The Ring Study, or IPM 027, in parallel with ASPIRE that will enroll approximately 1,950 women.

- Vaginal rings are flexible products that fit high up inside the vagina and are 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. As a potential method for preventing sexual transmission of HIV, rings are seen as an alternative to microbicide gels, which are intended to be used at the time of sex, some even daily. The dapivirine ring being tested in ASPIRE is designed to be used by women for four weeks at a time.

- ASPIRE represents a major step forward in the evaluation of a promising female-controlled method that potentially could provide women with discreet, long-acting protection. Building on IPM’s previous research and as a complement to The Ring Study, ASPIRE is a critical component in a strategy that seeks to license the dapivirine ring. Significantly, ASPIRE and The Ring Study are the first effectiveness trials of a vaginal ring for HIV prevention and of a product that contains an ARV other than tenofovir or a tenofovir combination.

WHY THIS STUDY IS IMPORTANT

Of the more than 34 million people living with HIV, half are women. Most women acquire HIV through heterosexual intercourse. In fact, women are twice as likely as men to acquire HIV during vaginal 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 eight times more likely to become infected with HIV than young men. Efforts to promote abstinence, monogamy and the use of male condoms have not been enough to stop the HIV epidemic nor are these practical methods in most settings. There is an urgent need for effective prevention strategies that women can control themselves, and that they are willing and able to actually use.
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 having been the most studied. In the CAPRISA 004 study, tenofovir gel used before and after sex reduced the risk of HIV infection by 39 percent compared to a placebo gel. However, tenofovir gel was not effective in another study called VOICE – Vaginal and Oral Interventions to Control the Epidemic – which was designed to test its daily use (as well as daily use of an ARV tablet). An analysis of blood samples at the end of the trial indicated that most women had not used their assigned study products daily as recommended. In the meantime, a Phase III trial, FACTS 001, is testing the same tenofovir gel regimen used in CAPRISA 004 (before and after sex), with results expected in 2015.

Experience in the area of female contraception has demonstrated that women’s preferences differ, and that a product that best suits a woman’s lifestyle and needs is more likely to be used. Only if a product is used and used properly does it have a chance of being effective. This is why it is important to investigate different HIV prevention strategies. Some women may prefer taking a tablet, or prefer using a vaginal microbicide gel; while others may prefer a vaginal ring that they replace monthly. ASPIRE is the culmination of a large body of research looking at the dapivirine ring as an alternative HIV prevention method for women. As sister studies, ASPIRE and The Ring Study are designed to provide the strength of evidence to support potential licensure of the product.

**HOW THE STUDY IS DESIGNED**

ASPIRE is a Phase III trial designed to evaluate the safety and effectiveness of the dapivirine vaginal ring for preventing the sexual transmission of HIV when used by women for one month at a time. The study will enroll up to 3,476 HIV-negative women who are randomly assigned to use either the dapivirine ring or a placebo ring that looks the same but contains no active drug. Participants learn how to insert and remove the ring when they first enroll into the study and receive additional guidance at monthly follow-up visits as needed. Women will replace their used ring with a new ring every four weeks over the course of at least one year, some for as long as two years. As part of the study, all participants receive ongoing HIV risk reduction counseling, condoms and diagnosis and treatment of sexually transmitted infections (STIs).

ASPIRE is also designed to assess women’s adherence to and acceptability of the ring. In women who acquire HIV during the study, researchers will try to determine if there is a relationship between drug levels in cells and tissues and HIV acquisition, as well as the nature and frequency of HIV drug resistance.

ASPIRE is being conducted at 15 sites in Malawi, Uganda, South Africa and Zimbabwe.

**ABOUT THE DAPIVIRINE RING**

Dapivirine, also known as TMC-120, is a type of ARV called a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs bind to and disable 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. As such, in 2004, IPM, a non-profit product development partnership based in Silver Spring, Md., received a royalty-free license to develop dapivirine for use as a microbicide in developing countries through an agreement with Janssen R&D Ireland. Since then, 16 clinical safety studies of dapivirine, formulated as either a vaginal gel or a vaginal ring, have been conducted by IPM and its partners.

The dapivirine ring is made of a flexible silicone material, similar to vaginal rings that are used for contraception and hormone replacement in the U.S. and Europe. Each ring contains 25mg of the ARV dapivirine. When placed inside the vagina, the ring releases the drug slowly over the four weeks that it is intended to be worn. Women then replace the used ring with a new one.

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Studies of the dapivirine ring have shown 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. Studies to date have also shown 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.

As part of its strategy to license the ring, IPM is conducting The Ring Study, also known as IPM 027, in parallel with ASPIRE. The Ring Study, which began enrolling women in April 2012, will collect additional long-term safety and efficacy data about the dapivirine ring among approximately 1,950 women at four sites in South Africa and one in Uganda. Several smaller studies of the ring are being planned, including studies that will be conducted by the MTN to evaluate the ring’s safety in adolescents and postmenopausal women, and others that IPM will be conducting looking at condom compatibility and drug interactions.

Should the dapivirine ring be found safe and effective, IPM will seek regulatory approval for product licensure and collaborate with key partners to help ensure the ring is made available to women in developing countries at low cost and as soon as possible.

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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.

More information and materials about ASPIRE is available at http://www.mtnstopshiv.org/news/studies/mtn020

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