Two Phase III Sister Studies of a Microbicide Ring to Prevent HIV:

The Ring Study and ASPIRE

Two Phase III studies — **The Ring Study** and **ASPIRE** — are being conducted across more than 20 sites in Africa to determine whether a monthly vaginal ring that releases an antiretroviral (ARV) drug called dapivirine prevents HIV infection in women and is safe for long-term use. Because women only need to replace the ring once a month, it could provide a discreet and easy-to-use new method of protection.

The Ring Study is being led by the nonprofit International Partnership for Microbicides (IPM), which developed the dapivirine ring. ASPIRE is being led by the US National Institutes of Health-funded Microbicide Trials Network (MTN).

Together, these "sister" studies involve more than 4,500 women volunteers across southern and eastern Africa, and are expected to provide the evidence needed to secure regulatory approvals and licensure for this new tool when all study results become available by 2016.

Because at least two Phase III efficacy trials are usually needed for a product to be considered for regulatory approval, IPM and MTN partnered to run these two sister studies concurrently to keep the timeline to potential approval and product access as short as possible. This is important given women's urgent need for new HIV prevention tools.

Why These Studies Are Important

- Of the more than 35.3 million people living with HIV, more than half are women. Women account for nearly 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual sex is the primary driver of the epidemic. Young women are especially vulnerable — women ages 15 to 24 are twice as likely as young men to be infected with HIV.

- Efforts to promote abstinence, monogamy and the use of male condoms have neither done enough to stop the HIV epidemic nor are they realistic methods in many settings. Women lack practical and discreet tools they can use to protect themselves from HIV infection.

- Vaginal rings are flexible products that fit comfortably high inside the vagina and provide sustained delivery of drugs over a period of time. Women in many countries already use vaginal rings designed to deliver contraceptive hormones. IPM's dapivirine ring adapts this commonly used medical technology to offer women potentially long-acting protection from HIV during sex with a male partner.

- The dapivirine ring is the first long-acting ARV-based product to enter efficacy testing and the first involving an ARV other than tenofovir or a tenofovir combination. As the product developer and regulatory sponsor, IPM will seek regulatory approval for the dapivirine ring based on the results of The Ring Study and ASPIRE as well as several smaller safety studies taking place in the United States and Europe. Together, all of these studies make up the full Dapivirine Ring Licensure Program.

- The Ring Study and ASPIRE are the first large-scale clinical trials of a vaginal ring for HIV prevention and represent a major step toward new, self-initiated HIV prevention options for women.

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How the Sister Studies Are Designed

The Ring Study and ASPIRE are, by design, similar in many ways. Both are Phase III trials designed to evaluate whether the dapivirine ring is safe and effective when used for one month at a time. Both studies are also assessing women's adherence to and acceptability of the ring.

Women who enroll in either study are randomly assigned to use either the dapivirine ring or a placebo ring (that looks the same but contains no active drug) throughout their time in the trial. Both studies are "double-blinded," meaning neither the women nor the researchers know which of the two rings participants have been assigned to use until after the studies are completed. Studies are blinded to ensure the scientific integrity of results.

Both studies include numerous measures to monitor and protect the safety and well-being of participants. Potential study participants provide informed consent to be screened and to enroll in the study. Women who choose to participate learn how to insert and remove the ring.

At each monthly visit, women receive a new ring. Women also receive ongoing HIV risk-reduction counseling, male condoms, diagnosis and treatment of sexually transmitted infections (STIs), pregnancy testing and family planning services, as well as treatment or referrals for medical conditions. Women in either study who test positive for HIV immediately stop using the ring and are referred to local health facilities for care and treatment, with an option to enroll in a follow-up study to assess the ring's impact, if any, on HIV treatment outcomes.

The Ring Study

- The Ring Study has enrolled 1,959 HIV-negative women, ages 18 to 45. Women are randomly assigned to use either the dapivirine ring or a placebo ring; for every two women using the dapivirine ring, one is using a placebo ring. Women use their assigned ring type for the entirety of the study. All women enrolled in The Ring Study are asked to use the monthly ring for two years because one of the study's main objectives is to evaluate the long-term safety of the ring.

- The Ring Study began enrolling women in the trial in April 2012. It is taking place at seven research centers in South Africa and Uganda. The study completed enrollment in November 2014 and is expected to conclude and release results by 2016.

- The Ring Study is being led by Annalene Nel, MD, PhD, IPM's chief medical officer, based in Cape Town, South Africa, and Saidi Kapiga, MD, ScD, MPH, scientific director, Mwanza Intervention Trials Unit, in Mwanza, Tanzania.

ASPIRE

- ASPIRE — A Study to Prevent Infection with a Ring for Extended Use — has enrolled 2,629 HIV-negative women, ages 18 to 45, who are randomly assigned in equal numbers to use either the dapivirine ring or a placebo ring. Women use their assigned ring for at least one year, some for more than two years.

- ASPIRE began enrolling women into the trial in August 2012. It is being conducted at 15 sites in Malawi, Uganda, South Africa and Zimbabwe. The study completed enrollment in June 2014 and is expected to conclude around July 2015, with results available by 2016.

- ASPIRE is being led by Jared Baeten, MD, PhD, of the University of Washington in Seattle, and Thesla Palanee, PhD, of the Wits Reproductive Health and HIV Institute, in Johannesburg, South Africa.

About the Dapivirine Ring

IPM is developing dapivirine for use as a microbicide through a royalty-free licensing agreement with Janssen Sciences Ireland UC. Dapivirine, also known as TMC-120, belongs to a class of ARVs called non-nucleoside

reverse transcriptase inhibitors (NNRTIs) that bind to and disable HIV's reverse transcriptase enzyme, a key protein needed for HIV replication.
The dapivirine ring is similar to vaginal rings that are used for hormone delivery in the United States and Europe. The dapivirine ring, made of a flexible silicone material, allows the drug to be slowly released from the ring over time. Studies have shown that the ring can deliver dapivirine to vaginal tissue for a month or longer, with minimal absorption elsewhere in the body. Studies to date have also shown that the dapivirine ring is safe and well-tolerated by women.

If the dapivirine ring is found to be 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 a low cost and as soon as possible.

About Microbicides

Vaginal microbicides are HIV prevention products being developed for 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 tenofovir gel being the most clinically advanced. In a trial called CAPRISA 004, tenofovir gel successfully reduced HIV risk by 39 percent among women who used the gel before and after sex compared to women who used a placebo gel.

However, in another study known as VOICE (Vaginal and Oral Interventions to Control the Epidemic), which was designed to evaluate daily use of tenofovir gel, as well as daily use of an oral ARV tablet, researchers found that while safe, none of the interventions tested were effective in protecting women against HIV and that most women had not used their assigned products daily as recommended.

A third efficacy trial of tenofovir gel, FACTS 001, is evaluating whether it can help prevent the sexual transmission of HIV when used before and after sex (the same regimen used in CAPRISA 004), with results expected in early 2015.

Experience in the female contraception field 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 correctly and consistently does it have a chance of being effective. This is why it is important to investigate different HIV prevention strategies. Some women may prefer using a vaginal gel around the time of sex or taking a daily ARV tablet, while others may prefer a vaginal ring that they replace monthly.

Learn more about **The Ring Study** at http://www.ipmglobal.org/the-ring-study and about **ASPIRE** at http://www.mtnstopshiv.org/news/studies/mtn020.

About the International Partnership for Microbicides

The International Partnership for Microbicides (IPM) is a nonprofit organization dedicated to developing new HIV prevention tools and other sexual and reproductive health technologies for women, and making them available in developing countries. IPM has offices in South Africa and the United States, and works with local research center partners as well as trial networks like the MTN to conduct clinical studies of its products. To learn more, please visit www.IPMglobal.org.

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 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.