



Sister Studies: The Ring Study and ASPIRE



In an important achievement for HIV prevention, two Phase III studies in Africa — **The Ring Study and ASPIRE** — have shown that a monthly vaginal ring containing the antiretroviral (ARV) drug dapivirine can help prevent HIV infection in women and is safe for long-term use. This is the first time two studies have confirmed statistically significant efficacy for a microbicide. The ring could provide a discreet and easy-to-use new method of protection for women at high risk of HIV.

The Ring Study (IPM 027) is led by the nonprofit International Partnership for Microbicides (IPM), which developed the dapivirine ring, and ASPIRE (MTN-020) was led by IPM's clinical trial partner, the US National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN).

Together, these “sister” studies have involved more than 4,500 women volunteers across southern and eastern Africa, and were designed to provide the evidence needed to seek regulatory approval for licensure of the ring.

Because at least two Phase III efficacy trials are usually needed for a product to be considered for regulatory approval, these two sister studies were designed to take place 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 they can and are willing to use.

Key Results

Results reported in February 2016 showed that:

- Overall HIV infections were reduced by 31 percent in The Ring Study and 27 percent in ASPIRE.
- ASPIRE showed a much higher level of protection for women over 21 — 56 percent — which was supported by a trend in The Ring Study exhibiting more protection for women in that age group, at 37 percent.
- Across both studies, women ages 18-21 showed little to no protection.
- In ASPIRE, women over 21 were more likely to use the monthly ring with consistency, which may help explain why protection was higher for them.
- The Ring Study showed a trend toward higher efficacy with more consistent ring use.
- Taken together, these data suggest that the ring needs

to be used consistently to achieve protection.

- The dapivirine ring is safe, with no statistical difference between active and placebo arms across both studies.
- Both studies found no evidence that use of the dapivirine ring increased the presence of ARV-resistant HIV virus.



Next Steps

- Pending approvals, IPM plans to conduct an open-label extension (OLE) study that would provide previous Ring Study participants with access to the dapivirine ring and help answer critical questions about the product and its use while it under regulatory review for licensure.

- The National Institute of Allergy and Infectious Diseases (NIAID), the primary NIH institute that funds MTN, has indicated it will convene a panel of outside experts to provide advice on the future of NIH-funded dapivirine ring research, including a similar OLE study for ASPIRE participants as well as a study aiming to better understand the HIV prevention needs of adolescent girls and young women under age 21.
- In parallel, IPM is also taking steps toward regulatory review to license the ring.
- IPM will work with governments and other partners to determine how the ring can best fit into comprehensive prevention programs, and to potentially get an affordable ring to women who could benefit from it.

Why These Studies Are Important

Women are at high risk for HIV infection: Of the more than 36.9 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 at greatest risk — women ages 15 to 24 are twice as likely as young men to have HIV.

Need for new prevention tools: 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 need a range of practical and discreet tools they can use to protect themselves from HIV infection.

Benefits of vaginal rings: 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 monthly protection from HIV during sex with a male partner. The novel ring is easy for women to insert and remove themselves.

Promising new technology: The dapivirine ring, which women insert and leave in place for one month, is the first discreet self-initiated HIV prevention method designed for women that has been shown to safely help offer protection over the course of a month. As the ring's developer and regulatory sponsor, IPM plans to 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. IPM is also building on the ring technology to develop next-generation and multipurpose products.

Pioneering HIV prevention research: 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.

Study Designs

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 also assess women's adherence to and acceptability of the ring.

Women enrolled in either study were 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 were "double-blinded," meaning neither the women nor the researchers knew which of the two rings participants have been assigned to use until after the studies are completed. Clinical studies are blinded to ensure the scientific integrity of results.

Both studies included numerous measures to monitor and protect the safety and well-being of participants. Potential study participants provided informed consent to be screened and to enroll in the study. Women who chose to participate learned how to insert and remove the ring.

At each monthly visit, women received a new ring. Women also received 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 tested positive for HIV immediately stopped using the ring and were 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 enrolled 1,959 HIV-negative women, ages 18 to 45. Women were 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. All women enrolled in The Ring Study 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 being conducted at seven research centers in South Africa and Uganda. The study completed enrollment in November 2014, and is scheduled to conclude in December 2016. In February 2016, The Ring Study began closing its placebo arm following feedback from regulatory authorities, based on the safety and efficacy findings from

both studies. All women still enrolled in the study will receive the active dapivirine ring for the remainder of their participation.

- The Ring Study is 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 — enrolled 2,629 HIV-negative women, ages 18 to 45, who were randomly assigned in equal numbers to use either the dapivirine ring or a placebo ring. Women used their assigned ring for at least one year.
- ASPIRE began enrolling women into the trial in August 2012. The study completed participant follow-up at 15 sites in Malawi, Uganda, South Africa and Zimbabwe in June 2015, and completed data analysis in November 2015.
- ASPIRE was 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.

Supporting Studies

The Ring Study and ASPIRE make up the centerpiece of IPM’s larger licensure program for the ring. To collect the safety data needed to obtain regulatory approval for the ring, IPM is also conducting a number of smaller safety studies, including:

Study	Description	No.	Status
IPM 007	Seroconverter protocol	n/a	Ongoing
IPM 013	Ring safety & PK	48	Completed
IPM 015	Ring safety	280	Completed
IPM 024	Ring safety & PK	16	Completed
IPM 028	Drug-drug interaction	36	Completed
IPM 029	Male condom functionality	70 couples	Completed
MTN-023/ IPM 030	Ring safety (adolescent girls)	96	Ongoing
MTN-024/ IPM 031	Ring safety & acceptability (post-menopausal women)	96	Data analysis
IPM 033	Female condom functionality	80 couples	Data analysis
IPM 034	Ring extended PK	40	Completed
IPM 035	Menses & tampon use	32	Ongoing
IPM 036	Drug-drug interaction	36	Ongoing
MTN-029/ IPM 039	PK (lactating women)	16	Planned

About the Dapivirine Ring

IPM, a nonprofit organization, is developing dapivirine for use as a microbicide through a worldwide rights agreement with Janssen Sciences Ireland UC, a Janssen pharmaceutical company of Johnson & Johnson. 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. IPM adapted the ring technology used for hormone delivery in the United States and Europe to develop the dapivirine ring. The ring, made of a flexible silicone material, slowly releases the drug over the course of a month, with minimal absorption elsewhere in the body. Studies to date have also shown that the dapivirine ring is safe and well-tolerated by women.

About Microbicides

Vaginal microbicides are HIV prevention products being developed for women to help reduce their risk of HIV infection through vaginal sex. Similar products are also being developed to prevent HIV transmission through anal sex.

To date, clinical trials have primarily focused on microbicides formulated as vaginal gels. In 2010, the CAPRISA 004 study showed that tenofovir vaginal gel reduced women’s risk of HIV infection by 39 percent when used before and after sex. Subsequent studies did not confirm these results. In 2013, the VOICE trial did not find the gel effective when used daily, likely due to low adherence. More recently, the FACTS 001 trial (2015) found the gel, when used before and after sex, also was not effective for the same reason.

These findings and those from the ring studies underscore the need for self-initiated products that women can and will use consistently. Stopping HIV will require a variety of effective products that match women’s individual needs and fit within the context of their lives. This is because existing HIV prevention options work for some — but not all — women. Condom use can be difficult for many women to negotiate. Research has shown that PrEP can be an effective prevention method for women, although continued research is needed on its use among young women. Although work remains to overcome adherence challenges seen in clinical trials of the ring and PrEP among young, high-risk women in Africa, both products could be important options for women. Research into other promising approaches in earlier phase testing, including long-acting injectable ARVs, new vaginal and rectal products, and vaccines, must also continue.

Learn More

The Ring Study: <http://www.ipmglobal.org/the-ring-study>

ASPIRE: <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 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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