

A Long-Acting Ring to Help Women Protect Themselves Against HIV

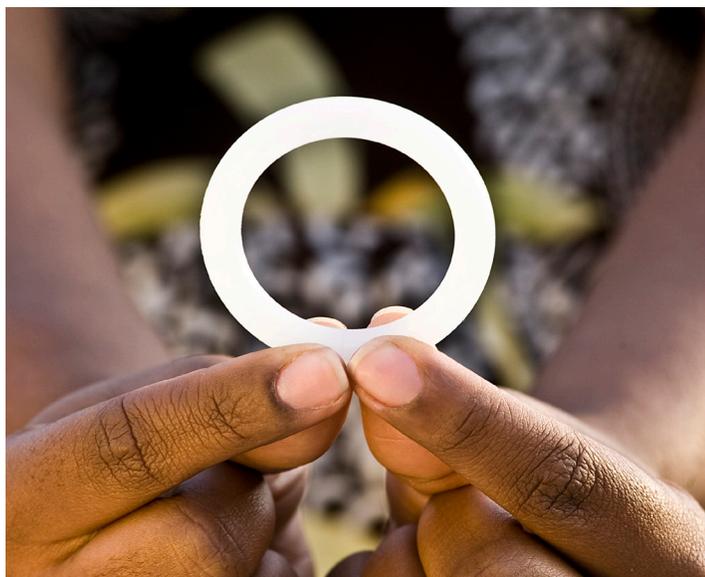


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New tools are urgently needed to bring down the persistently high infection rates among women. The monthly dapivirine ring, developed by the nonprofit International Partnership for Microbicides (IPM), adapts a medical technology commonly used to deliver hormones to women—a vaginal ring—to the effort against HIV.

Encouraging Results

Two Phase III studies found in 2016 that the monthly dapivirine ring reduced women's risk of HIV-1 infection by approximately 30% overall. Greater risk reduction was associated with increased use—HIV risk was cut by 45% among participants who used the ring at least some of the time. However, no reduction was seen in women under 21, likely due to low product use.



Together, the two studies evaluated monthly use of the ring in approximately 4,500 women ages 18-45 in Malawi, South Africa, Uganda and Zimbabwe. IPM led one of the Phase III studies, called The Ring Study, and our partner, the US National Institutes of Health-funded Microbicide Trials Network (MTN), led the other, called ASPIRE. IPM's dapivirine ring program also includes smaller studies required for regulatory approval.

OLE studies: Two subsequent open-label extension (OLE) studies, DREAM and HOPE, were conducted to offer the ring to former Ring Study and ASPIRE participants, respectively. In 2019, final results from the OLEs showed increases in ring use and modeling data suggest greater risk

reduction—by over 50% across both studies—compared to the Phase IIIs. Although these modeling results are limited due to the lack of a placebo comparison group, they indicate an encouraging trend we hope to see continue if the ring is approved and rolled out.

Status and Next Steps

Regulatory applications: The dapivirine ring is now under review by the European Medicines Agency for the product's use in developing countries, where women face the highest HIV risk, with a scientific opinion expected in 2020. IPM also plans to submit applications to the US Food and Drug Administration and the South African Health Products Regulatory Agency, followed by other national regulatory authorities in Africa. IPM is working across sectors to prepare for the ring's possible introduction, initially in eastern and southern Africa.

Other ring research: A three-year study called REACH began in 2019 to assess the safety, acceptability and use of the monthly dapivirine ring and a daily oral HIV prevention pill, known as PrEP, among young women and adolescent females ages 16-21 in South Africa, Uganda and Zimbabwe. In addition, two studies planned for 2019-2020 will assess the safety of the ring and PrEP among pregnant and breast-feeding women in Africa.

Need for New Options

Existing prevention tools are all necessary but have not stopped the epidemic's spread among women, particularly in sub-Saharan Africa, where young women are twice as likely as young men to acquire HIV. Women urgently need new options they can use on their own terms to meet their prevention needs, which can change throughout their lives.

Potential Public Health Impact

Modeling studies show that a combination approach is needed to end the epidemic—and that microbicides like the dapivirine ring could have a meaningful impact as part of that approach.

Long-acting and Discreet

The dapivirine ring marks the first time a vaginal ring has been shown to deliver an ARV for HIV prevention. If approved, the ring would be a valuable addition to the HIV prevention portfolio by offering women a long-acting tool they could use discreetly to help protect against infection.

Ring Technology: Slow-release and locally-acting

Vaginal rings provide controlled release of drugs over extended periods of time. IPM's ring is a novel formulation made of a flexible silicone material with 25mg of the ARV drug dapivirine dispersed uniformly throughout its matrix (56mm outer diameter, 7.7mm cross-sectional diameter). The ring delivers sustained-release of the drug directly to the site of potential infection over the course of a month, with low absorption elsewhere in the body, which could help minimize side effects.

Active Ingredient: Dapivirine

Dapivirine belongs to the same class of ARVs used to successfully treat HIV/AIDS and prevent mother-to-child transmission. Dapivirine is a type of ARV known as a non-nucleoside reverse transcriptase inhibitor that works by blocking HIV from replicating inside a healthy cell.

Janssen Sciences Ireland UC, a Johnson & Johnson company, first tested dapivirine in oral formulations in 11 safety studies before partnering with IPM, which has since tested dapivirine as a vaginal ring or gel in 30 clinical studies. Studies to date show dapivirine to be well-tolerated in healthy, HIV-negative women in Africa, Europe and the US.

Safety and Acceptability

- *Safety profile:* The Phase III studies showed the dapivirine ring was well-tolerated over long-term use, with no statistical difference between the active dapivirine group and the placebo group. In addition, 15 safety studies of different dapivirine ring formulations support the ring's tolerability profile.
- *Acceptability:* During the ring's early development, two IPM acceptability studies among women in Africa found the ring was acceptable, and nearly all women expressed interest in using the ring if proven effective. Many women in the Phase III studies reported forgetting the ring was in place, and that neither they nor their partner could feel it during sex.

A Product of Partnership

IPM pioneered the ring's development through public-private partnerships that brought scientific ingenuity, political will and financial resources to bear on all phases of product development.

The ring got its start in 2004, when IPM negotiated a royalty-free license with Janssen to develop dapivirine as

a microbicide for women in developing countries. That agreement expanded in 2014 to an exclusive worldwide rights agreement that ensures any future dapivirine product is available at low cost to women in resource-poor settings.

In cooperation with governments, foundations, researchers, industry, advocates and communities, IPM took the ring from concept through late-stage trials in 12 years. If the ring is approved for public use, it will be crucial to build on the global collaborations that got us to this point to finance and coordinate affordable access to the product.

From Concept to Results—and Beyond

- **2004:** IPM obtains dapivirine license and begins preclinical work
- **2005-2010:** IPM develops ARV ring, tests four prototypes and advances one to clinical trial program
- **2010-2012:** Four early-stage studies show the ring is well-tolerated and acceptable to women
- **2012:** Two Phase III studies launch in Africa
- **2016:** Phase III studies find IPM's dapivirine ring helped reduce women's HIV risk and was well-tolerated
- **2017:** First regulatory submission, ongoing research and preparations for possible introduction
- **2019:** Results from two open-label extension studies show increased ring use and suggest greater HIV risk reduction compared to Phase III studies

Building on the Monthly Ring

IPM is developing follow-on products such as a three-month dapivirine ring that could reduce annual costs and the number of provider visits needed to obtain the product, compared to the monthly version. It entered its first clinical trial in 2017, with results expected in 2019.

IPM is also developing a three-month ring designed to simultaneously prevent HIV and unintended pregnancy, two of the greatest threats to women's health in developing countries. Encouraging results from a first Phase I trial in 2017 led to a second one that began in 2018, with results expected in 2020.

Offering Women Hope

If approved, IPM's monthly dapivirine ring could fill an important gap with a long-acting prevention method for women who are unable to use higher-efficacy products like daily oral PrEP consistently. Controlling the epidemic will only be possible with a comprehensive HIV prevention portfolio that includes condoms, PrEP and TasP, future woman-centered products like rings and methods still being developed such as injectables, implants and vaccines.