

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

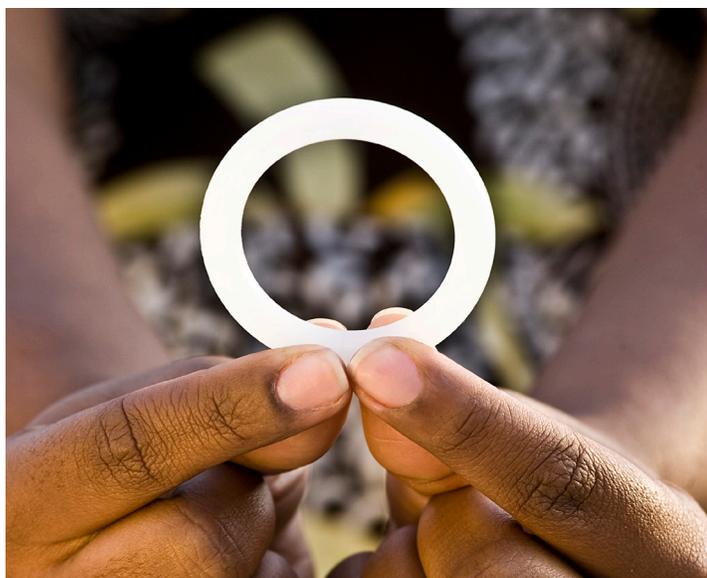


INTERNATIONAL  
PARTNERSHIP FOR  
MICROBICIDES

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

## Promising Results

Two Phase III studies found in 2016 that the monthly dapivirine ring reduced women's risk of HIV-1 infection by approximately 30 percent overall. Greater risk reduction was associated with increased use—HIV risk was cut by 45 percent among participants who used the ring at least some of the time. A 40 percent risk reduction was seen among women over 21, although 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 open-label extension (OLE) studies, DREAM and HOPE, began in July 2016 to offer the ring to former Ring Study and ASPIRE participants, respectively. Interim results from the OLE studies show encouraging

increases in ring use compared to the Phase IIIs and modeling data suggest greater risk reduction—by approximately 50 percent overall. More recent data from DREAM suggest a 59 percent reduction in HIV risk. HOPE completed in October 2018 and DREAM completed in January 2019, with final results for both studies expected in 2019.

## Next Steps

**Regulatory approval:** IPM is submitting applications to regulators to potentially license the dapivirine ring for use in developing countries, where women face the highest risk for infection. The dapivirine ring is now under review by the European Medicines Agency. IPM plans to submit applications to the South African Healthcare Products Regulatory Agency and the US Food and Drug Administration in 2019, followed by other national regulatory authorities in Africa. IPM is working across sectors to prepare for the ring's possible introduction.

**Upcoming research:** A study called REACH began in 2019 to assess the 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 Kenya, South Africa, Uganda and Zimbabwe. REACH, led by MTN, will look at preferences for each product, provide insights into barriers to their use and evaluate their safety among this high-risk population. In addition, two studies planned for 2019-2020 will assess the safety of the ring and PrEP among pregnant and breastfeeding women in Africa.

## Need for New Options

Existing prevention tools have not stopped the epidemic's spread among women and girls, particularly in sub-Saharan Africa, where young women are twice as likely as young men to become infected. Ending the epidemic will require a range of options that fit within the context of women's lives.

## Potential Public Health Impact

Modeling studies suggest that microbicides such as the dapivirine ring could have a meaningful public health impact as a valuable addition to current options.

## Benefits: Long-acting and discreet

The dapivirine ring, which IPM began developing in 2004, marks the first time a vaginal ring has been shown to deliver an ARV for HIV prevention. If approved, the ring would offer women a convenient and 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 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, 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

The ring's safety and women's preferences were prioritized from the outset.

- **Strong safety profile:** The Phase III studies showed the dapivirine ring was well-tolerated with 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.
- **Highly acceptable:** During the ring's early development, two IPM acceptability studies among women in Africa showed the ring is acceptable to them, and nearly all women expressed interest in using the ring if it is 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 about a decade. 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 novel 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 submissions, ongoing research and preparations for possible introduction
- **2018:** Interim results from open-label extension studies show increased ring use and suggest greater HIV risk reduction compared to Phase III studies

## Next-Generation Rings

IPM is developing next-generation products such as a longer-acting three-month dapivirine ring that could improve convenience and reduce annual costs compared to the monthly version. It entered its first clinical trial in 2017.

IPM is also developing a three-month ring designed to simultaneously prevent both 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 supported a second Phase I trial that began in 2018. Results from that second trial are expected in 2020.

## Offering Women Hope

HIV/AIDS remains one of the greatest threats to women's health globally. Women urgently need multiple options that they can use on their own terms to meet their prevention needs, which can change throughout their lives. If approved, IPM's monthly dapivirine ring could expand women's options with a self-initiated, long-acting new prevention method, complementing existing tools such as condoms and daily oral PrEP as well as products being developed such as injectables, implants and vaccines.