The Monthly Dapivirine Vaginal Ring: Frequently asked questions

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The dapivirine vaginal ring is an investigational product designed to reduce women's HIV risk and is currently under regulatory review in eastern and southern Africa and the United States. This document provides educational information about the ring and its next steps, and answers to frequently asked questions about the product.

Dapivirine Ring: The Basics

What is dapivirine?
Dapivirine is a potent ARV that belongs to a class of ARVs known as non-nucleoside reverse transcriptase inhibitors, or NNRTIs, which work against HIV-1 by blocking its ability to make copies of itself once inside a healthy cell. IPM began developing dapivirine as a microbicide in 2004, when it received a royalty-free license from the Janssen Pharmaceutical Companies of Johnson & Johnson, which was later expanded to a worldwide rights agreement.

What is the dapivirine ring?
It is made of a flexible silicone with 25mg of the ARV drug dapivirine dispersed uniformly throughout its matrix. The ring provides sustained release of the drug locally in the vagina over the course of a month with low exposure elsewhere in the body, which could help minimize side effects and reduce the risk of the development of HIV resistance.

Is the ring easy to insert and use?
Yes. A woman could insert the flexible ring easily herself and would replace it each month.

Can women feel the ring once it's inserted?
Women in studies to date overwhelmingly say the ring is comfortable and they cannot feel it once it's inserted and left in place. Some women reported being concerned initially about the size of the ring and how it would feel, but with education and experience, the vast majority of women could no longer even sense it was there after a brief period of time. A woman can go about her daily activities as usual.

How effective is the dapivirine ring?
Two Phase III efficacy studies found that IPM's dapivirine ring reduced women's HIV risk by about 30% overall with no safety concerns with long-term use. Notably, HIV risk reduction was likely greater among participants who used the ring more regularly. We are also encouraged that two subsequent open-label studies of the ring found increased product use and suggest greater risk reduction—by about half across both studies—compared to the Phase IIIs. Although the open-label results are estimates based on statistical modeling, they indicate a promising trend that was also seen with oral PrEP efficacy and open-label studies.

How safe is the ring?
There were no safety concerns with long-term use of the ring in two large Phase III trials, with no statistical difference in adverse events between the active dapivirine ring and the placebo groups. Data from two open-label studies show a similar favorable safety profile as do 12 smaller safety studies.

Does the ring have side effects? What are they?
Side effects in the Phase IIIs were generally mild to moderate genital and urinary tract issues that were minor and transient in most cases, and that resolved without interrupting ring use (for example, urinary tract infections, vaginal discharge or itching, and pelvic or lower abdominal pain). If the ring is approved for public use, women should contact their healthcare providers if they experience pain or discomfort or have any concerns.

How long does the ring need to be in place before it begins reducing her risk for HIV infection?
It's advised that the ring be in place for 24 hours. Because the levels of dapivirine drop quickly after ring removal, it's important that women keep the ring in place to ensure risk reduction is achieved, and then immediately replace it with a new one each month.

If a woman takes the ring out to clean it, how long does the HIV protection last? After she reinserts the ring, does she need to wait another 24 hours for the ring to provide protection again?
The precise period of 'forgiveness' following ring removal cannot be determined, although it's important to note that it is not necessary to remove the ring for cleaning or during menses. But yes, the ring should be in place for 24 hours after reinsertion before it can begin reducing HIV risk. Because vaginal fluid levels do drop quickly after ring removal, it is recommended that the ring be kept in place continuously for 28 days until it is replaced with a new ring.

Can a woman use the ring intermittently?
Intermittent use of the ring is not recommended. Intermittent use hasn't been studied and its efficacy is unknown. The ring must be in place to reduce HIV risk and is designed to be used continuously for one month. It is not necessary to clean or remove the ring during or after menses or sex, and sexually transmitted infections (STIs) can be diagnosed and treated without removing the ring.

Could the ring be used simultaneously with other HIV prevention products?
If approved, the ring should be used in combination with safer sex practices such as male or female condoms. However, IPM does not currently recommend simultaneous use of the ring and PrEP, as this has not been studied.

Would widespread use of the ring create resistance to treatment products in the same class?
This is an important issue that IPM will continue to study, including in ongoing and upcoming research. Data from the Phase III studies of the ring showed no evidence that the ring increased resistance to NNRTIs, the class of ARV drug to which dapivirine belongs and which is also used in some treatment regimens.

Does the ring protect against HIV during anal sex?
No. The monthly dapivirine ring is designed to reduce the risk of transmission of HIV through vaginal sex. Currently, condoms and oral PrEP are the only methods available to effectively prevent HIV transmission during anal sex as well as vaginal sex.

Does the ring prevent STIs other than HIV?
No. Condoms are currently the only product that can prevent HIV as well as other STIs.

Does the ring prevent pregnancy?
No, the monthly dapivirine ring does not act as a contraceptive in any way.

However, IPM is also developing a three-month ring that contains both dapivirine and a contraceptive hormone and is designed to reduce HIV risk and prevent unintended pregnancy simultaneously. The dapivirine-contraceptive ring is being studied in safety trials.

Can the ring be used with contraception?
If approved, the ring can be used with some forms of contraception, including male and female condoms, oral contraception, and hormonal injections and implants. The dapivirine ring should not be used with contraceptive vaginal rings or diaphragms.

Can the ring be used during a woman's period?
Yes. There is no need to remove the ring during menstruation. The ring should be kept in place for 28 days to ensure risk reduction and then replaced with a new one.

Does the ring protect both partners or only women?
The dapivirine ring only reduces the risk of HIV-1 transmission via vaginal sex for an HIV-negative woman. It does not provide protection for male partners.

How should the ring be disposed?
The ring should be wrapped in tissue or toilet paper and disposed of in a trash bin, out of the reach of children or pets.

Who funded the development of the ring?
IPM's work is made possible through the generous support of numerous donors. In addition, one of the Phase III ring trials and its open-label follow-on study (the ASPIRE and HOPE studies), as well as several safety studies, were conducted by MTN and funded by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all part of the U.S. National Institutes of Health (NIH).

Regulatory Status and Key Next Steps

What does the EMA's positive opinion mean for the monthly dapivirine ring and for women?
The opinion is a milestone for women at high risk for HIV. The EMA's opinion through Article 58 (now known as EU-Medicines for All or EU-M4all) is validation from a stringent regulatory authority that the monthly dapivirine ring could help fill a critical gap in the HIV prevention portfolio for women with a long-acting option. The positive EMA opinion opens the door to the next steps needed to seek approvals for the ring and make it available in countries where women are at high risk. IPM, which developed the monthly ring, will continue developing follow-on rings—including an even longer-acting three-month dapivirine ring as well as a three-month ring designed to offer simultaneous HIV prevention and contraception.

Who is the ring for?
The EMA provided a positive scientific opinion for the ring's use by women ages 18 and older in developing countries to reduce their HIV risk. In sub-Saharan Africa, women continue to bear the burden of the HIV

epidemic and continue to have an urgent unmet need for new HIV prevention options. The ring could give women a new choice for HIV prevention.

What is the Article 58/EU-M4all procedure?
Through Article 58/EU-M4all, the EMA, in cooperation with the World Health Organization (WHO), provides a scientific opinion on a product intended for use outside of the European Union—specifically to address a disease of major public health interest in developing countries. This procedure uses the same rigorous standards as for medicines intended for use in the EU. It involves experts from WHO and observers from national regulatory authorities in representative countries where a product may be used. A positive opinion from the EMA through Article 58/EU-M4all is recognized by many countries in Africa, which can facilitate regulatory reviews there, and it can shorten the timeline to WHO prequalification.

What is WHO prequalification? What does it mean for the ring?
In November 2020, the dapivirine ring received WHO prequalification, a designation that confirms the product meets global standards for quality, safety and efficacy and an important step toward making the ring available in Africa. The product's addition to the WHO's list of prequalified medicines will help guide national and global procurement decisions, pending country regulatory approvals for its use.

What does the WHO recommendation mean for the ring?
It means that the WHO recommends the ring as a new HIV prevention choice for women at substantial risk as part of a comprehensive HIV prevention strategy—which means the ring may be offered to women as part of a menu of product options and with the complete information they need to make an informed choice about the potential benefits and risks of all those options. Many countries use the WHO's recommendations and guidelines to inform their own policies.

Where could the ring be available first? Why did you select those countries?
We are prioritizing initial introduction of the ring in sub-Saharan Africa, where women have an urgent unmet need for new prevention choices. The countries selected for the first phase of introduction are Eswatini, Kenya, Lesotho, Malawi, Rwanda, South Africa, Tanzania, Uganda, Zambia and Zimbabwe. Given women's high risk, making the ring available across Africa is vital, and regulatory submissions to additional countries will follow as soon as possible.

What are the next steps for the ring's review in African countries?
IPM is submitting applications for the ring's use in Africa through the WHO's collaborative procedure that accelerates national regulatory reviews for a product that has already received a positive decision from a stringent regulatory body such as the EMA. Regulatory applications have been submitted to initial target countries (Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda, Zambia and Zimbabwe). IPM will also seek to make the product available in Eswatini and Lesotho through national import license processes, and expects to submit applications in additional countries in Africa in the future.

When could the ring be available to women?
Pending regulatory approvals, IPM hopes to begin making the ring available in some countries in eastern and southern Africa in 2021. The timing for each country will vary depending on a variety of factors, including regulatory reviews and approvals, national policy decisions, final packaging and supply chain logistics as well as any challenges to rollout posed by the COVID-19 pandemic.

Will the ring only be available in Africa or will it have a global reach?
In line with IPM's nonprofit mission, the first phase of the dapivirine ring's potential rollout is prioritized for

sub-Saharan Africa where it could have the greatest impact given the urgency of the epidemic in that region. However, we are open to providing the ring to women in any country in the future on the basis of need and demand. IPM holds exclusive worldwide rights to dapivirine through Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson. This agreement ensures that dapivirine-based products are first distributed in developing countries; however, the agreement also enables access to products in developed countries.

When are you submitting to the US Food & Drug Administration? How long will that review take?
IPM submitted an application to the US FDA in late 2020, which has a one-year review period.

Will IPM also seek approval for the ring's use among adolescent girls?
Yes. Addressing adolescent girls' urgent unmet HIV prevention needs is a high priority. Results from one completed study among adolescent girls and young women in the US (led by the US National Institutes of Health-funded Microbicide Trials Network [MTN]) and a two-year study now underway in Africa (REACH, also led by MTN) may support regulatory approvals in the future for the ring's use among this key group.

Why is the EMA looking for additional data among women ages 18-25?
In its positive opinion for the ring, the EMA noted the lower HIV risk reduction seen among women 18-21 due to low product use. The agency recommended a post-authorization study both to complement existing efficacy data and to better understand the ring's efficacy among younger women, who remain at alarming risk for HIV. The study will also offer an opportunity to learn how to support young women to use the ring now that they know that it received a positive regulatory opinion, and to maximize its effectiveness in the real world. The ongoing REACH study by MTN will also help us understand the ring's use among young women in addition to adolescent girls.

When will the post-authorization study begin?
Details about the study, including timelines, study design and location will require consultation as part of the ongoing EMA scientific advice procedure as well as with donors, governments, research partners, communities, women and civil society for their inputs. We will provide updates on our website as we have them.

Can pregnant and/or breastfeeding women use the dapivirine ring if it is approved?
There are limited data on the ring's safety among pregnant and breastfeeding women. Each country that approves the ring will develop its own clinical guidelines; one possibility is that women who are pregnant or breastfeeding would be advised to consult with their healthcare providers to discuss the potential benefits and risks of using the ring. Currently, IPM's partner MTN is conducting two studies (DELIVER and B-PROTECTED) on the ring's safety and use to help us understand how the ring and daily oral PrEP could fit into the lives of women in these key groups, who face an estimated two to four times higher risk of HIV. Results from those studies would inform clinical guidelines for the ring's use.

Planning for Ring Introduction

How does the ring fit into the existing HIV prevention portfolio?
As the first long-acting HIV prevention method, the dapivirine ring would help fill a critical gap in the prevention portfolio and offer women a monthly option they can control themselves and use when they are unable to, or choose not to, use daily oral PrEP. Women need different options so they can choose the most effective product that best meets their individual needs and life circumstances, which can also change over

time. Multiple modeling studies show that a combination prevention approach is needed to achieve epidemic control—that includes oral PrEP, treatment-as-prevention, condoms, male circumcision, plus woman-controlled tools like rings as well as future injectables and methods in development like rectal microbicides, implants and vaccines. No product is perfect, so offering all products is important to ensure every woman has a way to protect herself.

What is IPM doing to ensure women can access the ring when approvals are received?
IPM is working with a global network of partners across sectors to shorten the timeline between approval and the ring's introduction as much as possible. This includes engaging with partners in manufacturing, procurement and supply chain management; conducting research to inform education and demand creation among women, communities and healthcare providers; and working with policymakers and implementers to learn from the rollout efforts of other biomedical products.

Would women have to pay for the ring?
As a nonprofit, our goal is for the ring to be publicly funded and provided to women at low or no cost. The ring's ultimate cost will vary by country, and IPM is working with donors, governments, civil society and other partners to keep costs to women low.

Where would women get the ring—pharmacies, hospitals, clinics?
The ring's distribution would vary by country. Because the dapivirine ring contains an ARV drug and will require periodic HIV testing, a physician or nurse would prescribe the ring, and some countries may also allow other health workers such as pharmacists to dispense the product in the future. IPM is working with regulatory agencies, policymakers, health worker associations, implementing organizations, advocates and others to identify distribution channels.

Because IPM's license for dapivirine is through the Janssen Pharmaceutical Companies of Johnson & Johnson, do they get royalties? Does IPM?
No, neither Janssen nor IPM will receive royalties on the ring. In fact, our licensing agreement with Janssen ensures that dapivirine-based products are made available at affordable cost in any low-resource setting where they are approved for use.