

CONTACT: Lisa Rossi  
+1- 412-641-8940  
+1- 412- 916-3315 (mobile)  
rossiL@upmc.edu

## QUESTIONS AND ANSWERS

### HOPE – HIV Open-label Prevention Extension Study

#### HOPE in Context

- ▶ The dapivirine vaginal ring is the first biomedical HIV prevention product specifically for women that has been shown to be well-tolerated and to reduce the risk of acquiring HIV in two independently conducted Phase III trials – ASPIRE and The Ring Study. Across both studies, HIV risk was reduced by about 30 percent; higher levels of protection were seen in women who used the monthly ring most regularly. Together, the two studies involved 4,588 women in four African countries where HIV rates for women continue to be among the highest globally, with condomless vaginal sex being the primary driver of HIV transmission.
- ▶ [ASPIRE](#) was conducted by the National Institutes of Health (NIH)-funded Microbicide Trials Network ([MTN](#)), while its sister study, [The Ring Study](#), was conducted by the International Partnership for Microbicides ([IPM](#)), a non-profit organization that also developed the dapivirine ring and is seeking its regulatory approval. The ring, which women can insert and replace themselves, contains an antiretroviral (ARV) drug called dapivirine that is slowly released over the course of the month it is used.
- ▶ After ASPIRE and The Ring Study, former participants had an opportunity to use the dapivirine ring for an additional year through two open-label extension studies – HOPE for former ASPIRE participants and DREAM for women who participated in The Ring Study. Both studies were designed to provide additional information about safety and adherence and other issues important for broader implementation of the ring should it be approved.
- ▶ Final results of DREAM, reported in June 2019, and HOPE, reported in July 2019, found no safety concerns and that women were interested in and willing to use the ring, with adherence to ring use higher than in the parent Phase III trials. Taken together, HOPE and DREAM suggest HIV incidence was reduced by about half with use of the dapivirine ring in these studies.

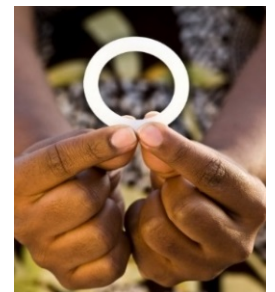
### HOPE – The HIV Open-label Prevention Extension Study

#### **What was the aim of the HOPE study?**

The [HOPE](#) study (HIV Open-label Prevention Extension, or MTN-025) was designed to provide former participants of the [ASPIRE](#) (MTN-020) Phase III trial the opportunity to use the dapivirine ring for one year while researchers collected additional information about its safety and how women would use the ring knowing that it was shown to reduce the risk of HIV in both ASPIRE and The Ring Study (IPM 027), a second Phase III trial that was led by the nonprofit International Partnership for Microbicides ([IPM](#)), which conducted a similar study called [DREAM](#) (IPM 032) for former Ring Study participants. IPM developed the dapivirine ring and is seeking its regulatory approval. The National Institutes of Health-funded Microbicide Trials Network (MTN) conducted ASPIRE and HOPE.

#### **What exactly is the dapivirine ring?**

The [dapivirine ring](#) is similar to vaginal rings commonly used for contraception except that it contains an antiretroviral (ARV) drug – dapivirine – instead, which gets slowly released into the vagina during the month that it is used. Women can insert and replace the dapivirine ring themselves. Dapivirine, also known as TMC-120, belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors that bind to and disable a key protein that HIV needs to make copies of itself. IPM holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen), which is designed to ensure that women in low-resource settings have affordable access to any dapivirine-based microbicide.



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### **Where was HOPE conducted and how many women enrolled?**

HOPE was conducted at 14 MTN-affiliated trial sites in Malawi, South Africa, Uganda and Zimbabwe where ASPIRE also took place, and enrolled 1,456 former ASPIRE participants, ranging in age between 20 and 49. To be eligible, women needed to be HIV-negative, not be pregnant or breastfeeding and agree to use contraception during the study.

### **When did HOPE take place?**

HOPE began in July 2016 and completed follow-up of participants in October 2018, after all women had the opportunity to use the dapivirine ring for one year.

### **Who led the study?**

Jared Baeten, M.D., Ph.D., of the University of Washington in Seattle, led the HOPE study, with Thesla Palanee-Phillips, MMed Sci, Ph.D., M.Sc., of the Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; and Nyaradzo Mgodzi, MBChB, MMed, from the University of Zimbabwe College of Health Sciences in Harare, Zimbabwe.

### **How was HOPE designed?**

As an open-label study, there was no placebo group in HOPE. All women, if they chose, received the monthly dapivirine ring. Other aspects of the study were designed to help move toward a more “real world” delivery model. For instance, visits were monthly for the first three months, and then quarterly thereafter. (At these quarterly visits, women were given the option of receiving three rings – one for each of the next three months.) Women in HOPE were free to choose to accept the ring or not, and to change their minds at any time during the study, without judgement. Moreover, women could enroll into the study even if they had no intentions or interest in using the ring. While staff counseled participants on the importance of adherence, they also wanted women to feel empowered to make their own choices and to be open about the reasons they may or may not want to or be able to use the ring.

### **Why did you enroll women who didn’t want to use the ring?**

By including all women, researchers hoped to better understand why the ring may work well as an HIV prevention strategy for some but not for others, how this might change over time or in different circumstances, and what factors influence women’s decisions about the ring. Such information could help other women use the ring successfully.

### **What are the results of HOPE?**

Final results of HOPE, which were reported in July 2019 at the 10<sup>th</sup> IAS Conference on HIV Science (IAS 2019) in Mexico City, found the dapivirine ring was well-tolerated, with no safety concerns – consistent with the safety profile seen in the ASPIRE Phase III trial; and women’s uptake and use of the ring (adherence) was higher. Results of HOPE also suggest lower than expected HIV incidence among participants. Specific findings are as follows:

- Uptake of the ring

At the start of HOPE, the majority of participants, 92 percent, accepted the ring. And, overall, interest in the ring was high throughout the one-year study. At three months, 87 percent of participants accepted the ring being offered to them. Thereafter, when women started coming to the clinic quarterly as opposed to monthly, interest declined only slightly, with 83 percent of women wanting the ring at month six and 79 percent of women accepting the rings being offered at month nine.

- Adherence

Measures of adherence, which look at the amount of drug remaining in rings participants returned at each clinic visit, indicate women’s use of the ring was higher in HOPE than it was in ASPIRE. In HOPE, 90 percent of returned rings indicated use compared to 77 percent in ASPIRE. Residual drug levels cannot determine how long the ring was actually used – for the full month, for example, or just a few days – and therefore are not an exact indication of adherence.

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- **HIV incidence**

Compared to ASPIRE, women's HIV risk appeared to be lower in HOPE. Of the 1,456 participants who enrolled in HOPE, 35 acquired HIV during the study, for an HIV incidence of 2.7 percent (for every 100 women followed during the one-year study there were 2.7 women who became newly infected). Using a method of statistical modeling that draws from the placebo group in ASPIRE, the researchers estimated HIV incidence would have been 4.4 percent had women not been able to take part in HOPE and be offered the ring, suggesting a 39 percent reduction in HIV risk.

### **What did the DREAM open-label study find?**

Final results of the [DREAM](#) (IPM 032) open-label extension study for former Ring Study participants, which were reported June 2019 at the 9<sup>th</sup> South African AIDS Conference in Durban, South Africa, also found higher uptake and adherence compared to the original Phase III study, with 95 percent of returned rings indicating some use, according to residual drug levels, up from 83 percent in The Ring Study. And using a similar modeling technique, results suggest women's HIV risk was reduced by 63 percent.

IPM conducted DREAM at six former Ring Study sites in South Africa and Uganda among 941 former participants of The Ring Study. Unlike HOPE, DREAM only enrolled women who agreed to use the ring during the study. DREAM was conducted between July 2016 and January 2019. All participants were followed approximately 12 months.

### **Why the difference in results between the HOPE and DREAM studies?**

Both research teams caution that without a true placebo group in either study, the results of the open-label extension trials cannot be viewed with the same degree of confidence as those from the earlier Phase III trials in which women were randomized to use either the active ring or a placebo ring. As such, the results of the DREAM and HOPE studies can only be considered estimates. What's important is that these estimates suggest a higher level of protection than in the Phase III trials, and researchers are encouraged that, together, the HOPE and DREAM open-label studies suggest HIV incidence was reduced by about half with use of the dapivirine ring in these studies.

### **How do the results of HOPE and DREAM compare to the parent Phase III trials?**

In the [ASPIRE](#) and [The Ring Study](#) Phase III trials, the results of which were reported at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2016 and published in the [New England Journal of Medicine](#), the ring was found to be well tolerated and reduced women's risk of acquiring HIV by about 30 percent overall (by 27 percent in ASPIRE and by 31 percent in The Ring Study). Higher levels of protection were seen in women who used the ring most regularly.

ASPIRE enrolled 2,629 sexually active HIV-negative women ages 18-45, and was conducted between August 2012 and June 2015 at 15 clinical research sites in Malawi, Uganda, South Africa and Zimbabwe. The Ring Study, which also began in September 2012, enrolled 1,959 HIV-negative women ages 18-45 at seven sites in South Africa and Uganda.

### **Is there need for the dapivirine ring when PrEP is already approved in many countries?**

Daily use of an ARV tablet called Truvada (oral PrEP) is an approach now approved in many countries, including in Africa, and recommended by WHO for persons at substantial HIV risk. PrEP is highly effective with consistent use. But daily pill-taking can be challenging for some people or not desired. Likewise, using a monthly vaginal ring may not be for everyone either. No single method will suit everyone, nor suit everyone at all times. As with contraception, the more HIV prevention options available to women, the more likely one will and can be used.

If approved, the monthly dapivirine ring would be the first biomedical HIV prevention product developed specifically for women – and the first long-acting product. Importantly, it would represent another option from which they may choose. Globally, more than half of all people currently living with HIV are women, and in sub-Saharan Africa, women account for nearly 60 percent of adults with HIV, with condomless vaginal sex the primary driver of the epidemic. Women need and deserve a range of safe and effective approaches to protect themselves against HIV.

## **At the Trial Site**

### **What approvals were needed to conduct HOPE?**

HOPE underwent extensive and rigorous review by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the U.S. Food and Drug Administration (FDA). Moreover, before any site could begin the study, approvals were required of government and drug regulatory authorities in the trial site country and by the site's Institutional Review Board (IRB) or Ethics Committee (EC). IRBs and ECs ensure that studies are scientifically valid and ethically sound, and provide oversight throughout the duration of the trial.

### **Did women participating in HOPE provide informed consent?**

Yes. As with any research study, women who volunteered to join HOPE were informed about all study procedures, possible risks and time requirements. Study staff also explained that women did not have to take part in the study and could leave it at any time, without consequence.

### **Was safety monitored in HOPE?**

Although ASPIRE and The Ring Study showed the dapivirine ring to be well-tolerated and to have a strong safety profile, one of the reasons for conducting HOPE was to collect additional information about the ring's safety. Women were monitored in much the same way as they were in ASPIRE, with routine laboratory tests, including HIV testing, and assessment of any ongoing or recent medical conditions at each study visit. Unlike ASPIRE, which involved monthly visits throughout the study, women in HOPE were seen monthly for the first three months, and then visited the clinic quarterly (every three months) thereafter. Participants with special concerns or needing more immediate attention could contact the trial site at any time.

### **Was oral PrEP offered to participants in HOPE?**

PrEP was not provided to participants as part of the study. However, women were counseled on oral PrEP as an HIV prevention option, and those who wanted to use PrEP were referred by trial sites to local programs, if and where available. Women could remain in HOPE if they chose to access oral PrEP, and could use PrEP concurrent to ring use if this was their preference.

### **What happened if a participant acquired HIV while in HOPE?**

Women in the trial who tested positive for HIV stopped using the ring immediately and were counseled and referred by study staff to local HIV care and support services. Women were encouraged to remain in the study and continue with routine study visits but were also invited to participate in another MTN study called MTN-015. MTN-015 does not provide HIV treatment, but offers laboratory tests indicating how the infection is progressing and how women are responding to treatment. Results from these tests may help local treatment providers better manage their clinical care.

### **What were the medical benefits for women participating in HOPE?**

Study participants received free laboratory tests and physical and pelvic exams, HIV prevention counseling and free condoms. Risk-reduction counseling, testing and treatment for sexually transmitted infections (STI) were also provided at no charge to women, and HIV testing and STI treatment was offered to their partners. In addition, HOPE provided effective barrier and hormonal contraception and monthly pregnancy and HIV testing. Women were referred to local service providers for ongoing treatment, management and care for any medical issues that could not be managed at the clinical research site.

### **How will women be protected from HIV now that they are no longer in HOPE?**

The reality is that participants live in areas where the risk of acquiring HIV is very high, and their options for protection are limited. That is exactly why researchers are doing this work – to expand the prevention options available to women. Before exiting the study, participants received counseling on different HIV prevention options, including how to access certain services after they leave the study. Options include: using condoms, using oral PrEP (if accessible), reducing their number of sexual partners, engaging in lower-risk sexual behaviors, having frequent HIV and STI testing (and receiving treatment for STIs, if infected), and encouraging their partners to be tested and treated for HIV and STIs and adhere to treatment regimens if HIV-positive.

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## **Next steps for the dapivirine ring**

### **What are IPM's plans for seeking regulatory approval of the dapivirine ring?**

IPM is seeking regulatory approval of the dapivirine ring for women ages 18-45. IPM's first application was submitted to the European Medicines Agency (EMA), under a procedure called Article 58 in which the EMA, in cooperation with the World Health Organization (WHO), is asked to provide a scientific opinion on the safety, efficacy and quality of the dapivirine ring for use specifically in low- and middle-income countries. Should the EMA grant a favorable opinion, IPM will then seek WHO pre-qualification. This is important because drug regulatory authorities in many developing countries often rely on WHO pre-qualification to determine which new products or drugs to consider for approval. If WHO pre-qualification is granted, IPM will proceed with applications to drug authorities in several African countries, including countries where ASPIRE and The Ring Study were conducted.

Separately, IPM plans to submit applications to the South African Health Products Regulatory Authority (SAHPRA) and to the U.S. Food and Drug Administration (FDA).

Each application, or dossier, that IPM submits to regulatory authorities will include data from more than 250 laboratory and clinical studies, detailing nearly 15 years of research. What was sent to the EMA, for example, was more than 260,000 pages. Applications being prepared for other regulatory submissions are likely to be of similar length and complexity. Moreover, because dapivirine is a new drug, the review process may be more complex and take longer than for a drug like Truvada, which was already approved for the treatment of HIV when it was under review for use as prevention, an approach called pre-exposure prophylaxis, or PrEP.

### **If the ring is approved, when and where will it be available?**

Exact timelines cannot be predicted. But if the ring is approved, IPM has indicated that it would prioritize rollout in sub-Saharan Africa, where women are at the greatest risk of HIV.

### **What role does the MTN play?**

The MTN is a clinical trials network that receives its funding from the NIH for the expressed purpose of designing and conducting the kind of studies needed to support potential licensure and regulatory approval of promising HIV prevention products. In this regard, the MTN has supported the regulatory process by conducting several key studies of the dapivirine ring that are included in the dossier of data that IPM is submitting to regulatory authorities.

In addition to the ASPIRE Phase III trial, these studies include five that were conducted in the United States: [MTN-023/IPM 030](#), a Phase IIa safety study of the ring in adolescent girls; [MTN-024/IPM 031](#), a Phase IIa safety study of the ring in post-menopausal women; [MTN-012/IPM 010](#), a Phase I penile safety study of dapivirine involving sexually abstinent men; [MTN-029/ IPM039](#) a safety and pharmacokinetic study of the dapivirine ring in lactating women; and [MTN-013/IPM 026](#), which collected data on the safety and pharmacokinetics of the dapivirine ring as well as a ring containing both dapivirine and a second ARV called maraviroc.

### **Are additional studies of the dapivirine ring being planned?**

Yes. The MTN is conducting additional studies of the dapivirine ring that intend to inform future potential approval of the dapivirine ring for girls under age 18 and for women during pregnancy and breastfeeding – populations of women who are especially vulnerable to HIV. In many parts of Africa, for example, it is estimated that 1,000 girls ages 15-24 are infected every day. Moreover, recent data suggest that when women are pregnant or breastfeeding, their risk of acquiring HIV is two to four times greater than when they are not.

- [REACH](#) (MTN-034) is an ongoing study evaluating both the ring and oral PrEP in young women and girls ages 16-21 at four sites in Kenya, South Africa, Uganda and Zimbabwe. Specifically, REACH looks to understand how young women use the monthly dapivirine vaginal ring and Truvada as daily PrEP, and their preferences for either or both approaches; and will collect information on the safety of these methods in young women. The study, which began in February 2019, will enroll 300 young women and girls and is expected to take about three years to conduct. All participants will use each product for six months. After experiencing both approaches, participants will have a choice of using either the ring or PrEP – or neither – for an additional six months.



Likewise, the DELIVER (MTN-042) and B-PROTECTED (MTN-043) studies are designed to assess the safety of the dapivirine ring and oral PrEP in pregnant and breastfeeding women. DELIVER and B-PROTECTED are expected to begin later this year (2019) at sites in Malawi, South Africa, Uganda and Zimbabwe.

- [DELIVER](#) will enroll 750 women at different times during pregnancy, who will use either the monthly dapivirine vaginal ring or Truvada as daily PrEP until the time they deliver. The study will be conducted in a stepwise, backward fashion, beginning with women late in pregnancy. Of the 750 women who will be enrolled, 500 will use the vaginal ring. The study is the first to be conducted of the dapivirine ring during pregnancy.
- [B-PROTECTED](#) will evaluate whether the dapivirine ring and PrEP are safe to use by women who are breastfeeding and will enroll up to 200 mothers and their breastfed babies between 6-12 weeks of age. Women will use their assigned product – PrEP or the dapivirine ring – for three months and be followed for an additional two weeks.

### **What about next generation rings?**

While a ring used for a month at a time may appeal to some women, others may prefer a product they replace every three months, or a ring that provides contraception in addition to protecting against HIV. Studies of these next generation rings include a study of a three-month ring (MTN-036/IPM 047) and studies of the dual-purpose ring (MTN-030/IPM 041, MTN-044).

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More information about HOPE and other MTN studies are available at <http://www.mtnstopshiv.org/news/studies>

More information about the dapivirine vaginal ring is available at <https://www.ipmglobal.org/content/ring-background-0>

### **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 <http://www.mtnstopshiv.org>.*