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QUESTIONS AND ANSWERS

Next Steps and Planned Studies of the Dapivirine Vaginal Ring

Summary and Fast Facts

- The dapivirine vaginal ring is the first biomedical HIV prevention product specifically for women shown to be safe and to reduce the risk of acquiring HIV in two independently conducted Phase III trials. Higher levels of protection were seen in women who used the monthly ring most regularly. Together these two studies involved more than 4,500 women in four African countries where HIV rates for women continue to be among the highest globally, with heterosexual intercourse 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.
- IPM is seeking its regulatory approval for women ages 18-45 based on the results of ASPIRE and The Ring Study and several supporting studies, including studies conducted by the MTN. The first decisions could be received in 2019.
- Additional studies of the ring are taking place or being planned by the MTN in parallel with regulatory submissions:
  - HOPE, an open-label extension study for former participants of ASPIRE, will help understand issues important for broader implementation of the dapivirine ring should it be approved.
  - The REACH study will involve adolescent girls and young women, while other studies are being planned in pregnant and breastfeeding women**.** Next generation dapivirine rings are also being evaluated – rings that can be used for up to three months and dual-purpose rings that include contraception.

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. Dapivirine 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. The ring, which is made of a flexible material, sits high inside the vagina, where it slowly releases the drug over the course of the one month the ring is worn. Women can insert and remove it themselves. 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.

Ring Results Recap

Primary results of both ASPIRE and The Ring Study, which were reported in February 2016, found the ring was safe 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. In fact, the ring was not effective among younger women ages 18-21 who used the ring least regularly. Results of an exploratory analysis of ASPIRE data reported at AIDS 2016 found the level of HIV protection for those who appeared to use the ring most consistently was at least 56 percent and as high as 75 percent or more with near perfect use.

ASPIRE was conducted at 15 clinical research sites in Malawi, South Africa, Uganda and Zimbabwe and involved 2,629 sexually active HIV-negative women ages 18-45. The Ring Study enrolled 1,959 women and was conducted at seven sites in South Africa and Uganda.

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HOPE – The HIV Open-label Prevention Extension Study

What is the aim of the HOPE study?
HOPE (HIV Open-label Prevention Extension, or MTN-025) was designed to provide former ASPIRE participants the opportunity to use the dapivirine ring in the context of a study. HOPE will build on the results of ASPIRE by collecting additional information on the ring's safety, how women use the ring knowing that it can help reduce their risk of HIV and the relationship between adherence and HIV prevention. HOPE also seeks to understand the reasons why some women choose not to enroll in the study, and why some who choose to enroll do not want to use the ring. By including all women, researchers hope 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 influences women's decisions about the ring. A similar study, called DREAM, is being conducted for former participants of The Ring Study.

Where is HOPE being conducted?
The MTN is conducting HOPE at 14 trial sites in Malawi, South Africa, Uganda and Zimbabwe where ASPIRE was conducted. Jared Baeten, M.D., Ph.D., of the University of Washington in Seattle, is leading HOPE, with Thesla Palanee-Phillips, Ph.D., M.Sc., of the Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; and Nyaradzo Mgodi, MBChB, MMed, of the University of Zimbabwe College of Health Sciences in Harare, Zimbabwe.

When did HOPE start, and when is it expected to be completed?
HOPE enrolled its first participants in August 2016 and completed formal enrollment mid-September 2017. The study expects to complete all follow-up in September 2018 and report results about six months later, in early 2019, within the same timeframe that the first decisions about regulatory approval of the ring could also be available.

How is HOPE designed?
In ASPIRE, participants were using a vaginal ring for the first time and had no knowledge of its efficacy or long-term safety, nor whether they had been randomly assigned to use the dapivirine ring or a placebo ring (that looked the same but had no active drug). In HOPE, there is no randomization and no placebo ring. All women, if they choose, receive the dapivirine ring. Women periodically receive their individual test results to help facilitate discussion about adherence and how it relates to protection. Visits are monthly for the first three months and quarterly thereafter – a schedule more in keeping with a public health service delivery model.

Is the expectation that women will use the ring more consistently in HOPE?
Participants in ASPIRE were using a vaginal ring for the first time, and they didn't know whether the ring was safe and effective or whether they had been assigned to use the active ring or the placebo ring. These uncertainties may have influenced willingness to the use the ring. Researchers are hopeful that women will feel more at ease about the ring in HOPE and that those who choose to accept the ring will use it as consistently as possible, knowing that its regular use can reduce their risk of HIV. In similar open-label extension studies of daily oral PrEP, adherence to product use increased, and as a result, the level of effectiveness was higher than in the original Phase III trials. At the same time, women in HOPE are free to choose the ring or not, and to change their minds at any time during the study, without judgement.

Why enroll women who don't want to use the ring?
By including all women, researchers hope 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. All participants who join HOPE contribute valuable information to the study, including how to help women use the ring successfully in the future.

About the regulatory approval process

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, the same age group represented in the ASPIRE and The Ring Study Phase III trials and among whom there is the most data. IPM's first application was submitted to the European Medicines Agency (EMA) in June 2017, under a procedure called Article 58 in which the EMA, in cooperation with the World Health Organization (WHO), provides a scientific opinion on the safety, efficacy and quality of the dapivirine ring. 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.

Separately, IPM plans to submit applications to the South African Health Products Regulatory Authority (formerly the Medicines Control Council) in early 2018 and to the U.S. Food and Drug Administration (FDA) later that year. If WHO pre-qualification is granted, IPM will also proceed with applications to drug authorities in several African countries, including Malawi, Uganda and Zimbabwe – where, in addition to South Africa, either ASPIRE or both ASPIRE and The Ring Study were conducted.

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

Daily use of an ARV tablet called Truvada for HIV prevention (often referred to as PrEP, or oral pre-exposure prophylaxis) is an approach now approved in many countries, including South Africa, Kenya and Zimbabwe, and recommended by WHO for persons at substantial HIV risk. PrEP is highly effective, but only with consistent use. Taking a daily tablet can be difficult for some people. Others may have concerns about the stigma associated with taking an ARV pill. But 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 method. 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 unprotected heterosexual sex the primary driver of the epidemic. Women need and deserve a range of safe and effective approaches to protect themselves against HIV.

What role, if any, does 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. The MTN plays no role in the regulatory process. But for its part, the MTN conducted 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 those 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; and MTN-012/IPM 010, a Phase I penile safety study of dapivirine involving sexually abstinent men.

The MTN has also completed a study that assessed whether dapivirine is absorbed in breastmilk and is now planning studies of the ring in breastfeeding and pregnant women in Africa. Its REACH study involving adolescent girls and young women will launch by mid-2018. Data from these studies will not be part of IPM's initial regulatory submissions but will be provided to regulators when they become available so that the ring can be considered for these important populations who are especially vulnerable to HIV.

Will the HOPE or DREAM open-label extension studies contribute to potential dapivirine ring approval?
IPM is submitting its applications to regulatory authorities as HOPE and DREAM are ongoing. Data from these studies will not be required of regulators in their review. IPM will, however, provide this information upon the studies' completion or, if requested by regulators, during the review process. Both studies will provide important information that will help guide implementation of the ring should it receive regulatory approval.

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When is a decision expected?
IPM is hopeful that the first regulatory approvals in Africa could be received in 2019. If the ring is approved by the EMA, and WHO has provided pre-qualification, IPM will move quickly to seek approval in other African countries. Timelines for potential approval will likely vary from country to country. Consider that the application, or dossier, that IPM submitted to the EMA included data from more than 250 laboratory and clinical studies, detailing nearly 15 years of research into 260,000 pages. Applications being prepared for other regulatory submissions are likely to be of similar length and complexity. 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, or PrEP.

If the ring is approved, when and where will it be available?
The first phase of the dapivirine ring's rollout would be in sub-Saharan Africa. But, while IPM hopes the first regulatory approvals are received 2019, at the soonest, approval would not mean the ring's immediate availability. Governments would still need to decide how they want to implement its delivery, and timelines and processes may differ across countries.

How much is the ring expected to cost?
If approved, the ring would likely be publicly funded and provided to women at low or no cost, similar to other HIV prevention services. Initially, IPM expects the cost per monthly ring to be approximately 7 USD, or 84 USD per year for 12 rings. Because such costs would be borne by governments and donors, the ring would be made available to women for free or at very low cost.

Studies in young women, pregnant and breastfeeding women and next-generation rings

What is REACH, the study involving adolescent girls and young women?
REACH (Reversing the Epidemic in Africa with Choices in HIV prevention, or MTN-034/IPM 045) is a study that seeks to understand the HIV prevention needs and preferences of adolescent girls and young women, who are among those at highest risk of HIV in sub-Saharan Africa. Specifically, the study will evaluate how adolescent girls and young women use the monthly dapivirine vaginal ring and Truvada as daily PrEP, and their preferences for either or both approaches, and collect information on the safety of these approaches. The study will involve 300 girls and young women ages 16-21 at five MTN-affiliated sites in Kenya, South Africa, Uganda and Zimbabwe. Lulu Nair, MBChB, MPH, of the Desmond Tutu HIV Foundation in South Africa is leading the REACH study, with Connie Celum, MD., MPH (University of Washington, USA) and Kenneth Ngure, PhD (Jomo Kenyatta University of Agriculture and Technology, Kenya).

Why is REACH important?
Adolescent girls and young women are among those most vulnerable to HIV in sub-Saharan Africa. While PrEP and the dapivirine ring, should it receive regulatory approval, could help curtail the rate of new infections, neither approach can be effective if not used consistently. Daily pill-taking was challenging for young women in clinical trials of PrEP. And while the monthly ring helped protect against HIV among women older than 21 in ASPIRE, it was not effective among those 18-21, who used the ring least consistently. Researchers need to understand the challenges young women face in using these products so strategies can be identified that can help. Even so, for oral PrEP and the dapivirine ring to be made available to girls under the age of 18, national regulatory bodies and HIV programs need to be assured of the safety of these approaches in this population. To date, there is very little safety data on oral PrEP and no safety data on the ring in younger African women. The MTN has already found the ring to be safe and acceptable to use by adolescent girls in a U.S. study called MTN-023 /IPM 030. REACH will contribute important information about the ring in African girls.

When will REACH start and be completed?
The study is expected to start early 2019, pending ethics committee and in-country approvals, and should take approximately three years to complete. Results are anticipated in 2020.

Are studies being planned of the dapivirine ring in breastfeeding and pregnant women?
The MTN recognizes the need for information about the safety of the ring in women during pregnancy and breastfeeding, because if the ring is approved, its intended use will be for sexually active women ages 18-45 – women of reproductive age.

As a first step, the MTN conducted a safety study (MTN-029/IPM 039) in the United States, which found only a very small amount of dapivirine is absorbed into breastmilk. Encouraged by these results, MTN is planning additional studies to be conducted in Africa. MTN-041 will explore attitudes about ring and PrEP use during pregnancy and breastfeeding among women currently or recently pregnant or breastfeeding, male partners and community stakeholders. MTN-042 proposes to evaluate the safety of the ring as well as oral PrEP in pregnant women, while MTN-043 would evaluate use of the ring in women who are breastfeeding. Researchers expect to launch these studies in 2018.

What about next generation rings – rings that are longer acting or that include contraception?
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. Toward this end, the MTN is evaluating IPM's next generation of dapivirine rings. MTN-030/IPM 041 is the first study of a dual-purpose ring containing both a hormonal contraceptive (levonorgestrel) along with dapivirine, in quantities large enough to feasibly provide protection from HIV and unintended pregnancy for up to three months. As a Phase I study, participants will use the ring for 14 days so that researchers can assess safety and how each active ingredient is taken up in the body in the presence of the other. A second Phase I study, called MTN-036/IPM 047, is evaluating a three-month dapivirine-only ring.

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More information about MTN studies is available at http://www.mtnstopshiv.org/news/studies

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.

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