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HOPE and Beyond:
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 ring most regularly. Together these two studies involved 4,588 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.
- The ring, which women can insert and replace themselves, contains an antiretroviral (ARV) drug called dapivirine that is slowly released during the month it is worn. IPM is seeking its regulatory approval for women ages 18-45 based on the results of ASPIRE and The Ring Study and of several supporting studies, including studies conducted by the MTN. A decision could be received late 2018 or early 2019.
- In parallel, additional studies of the ring are taking place or being planned by the MTN. 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. Other studies will collect data to support its use in adolescent girls and young women (REACH) and in pregnant and breastfeeding women.

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 HOPE, 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.

What exactly is the dapivirine ring?

The dapivirine ring is similar to vaginal rings commonly used for contraception except that it contains an ARV drug instead. Each ring contains 25 mg of the ARV dapivirine, about 4 mg of which gets released into the vagina over the month that it is worn. The ring, which is made of a flexible material, sits high inside the vagina. Women can insert and remove it themselves.

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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.

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, from 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 will complete 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.

What were the results of ASPIRE?
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, South Africa, Uganda and Zimbabwe. Primary results of both ASPIRE and The Ring Study were reported in February 2016. Overall, the two studies 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. 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.

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 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.

How is DREAM, the open-label access study for The Ring Study, different from or the same as HOPE?
As an open-label extension study for former participants of The Ring Study, DREAM (Dapivirine Ring Extended Access and Monitoring) is very similar to HOPE. It, too, is designed to collect additional safety information, explore when, why and how women use the ring, and to help understand how adherence may affect the product's efficacy. Both studies are also interested in understanding why some women do not want to use the ring. Unlike HOPE, the DREAM study will enroll an additional group of participants – about 600 young women ages 18-25 who are using the ring for the first time. In addition, IPM is currently working to identify funding so that it can continue DREAM beyond its first year (the study started July 2016). Pending this additional funding, DREAM could continue until a regulatory decision is made, and, if the ring is approved, until the product is available.

Why is participation in HOPE limited to one year?
HOPE is similar to other HIV prevention open-label extension studies conducted to date, which lasted between one and two years. In designing HOPE, researchers determined that a one-year follow-up period, during which former ASPIRE participants could use the ring, would provide answers to the study's questions within a timeframe that could help inform ongoing regulatory submissions, and if the ring is approved, its roll-out into communities.

About the regulatory approval process

What are IPM's plans for seeking regulatory approval of the dapivirine ring?
IPM intends to seek regulatory approval of the dapivirine ring for women ages 18-45, the same age group in the ASPIRE and The Ring Study Phase III trials and among whom there is the most data. IPM's first application will be to the European Medicines Agency (EMA), which is planned for mid-2017, followed by the South African Medicines Control Council (MCC) likely in late 2017. Approval will also be sought from the U.S. Food and Drug Administration (FDA) in early 2018.

As part of its submission to the EMA, IPM will apply for World Health Organization (WHO) pre-qualification, a process in which WHO determines whether a new drug or product meets global standards for quality, safety and efficacy. 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 the EMA approves the dapivirine ring and WHO provides pre-qualification, IPM will proceed with applications to drug authorities in several African countries, including Malawi, Uganda and Zimbabwe, where ASPIRE and The Ring Study were conducted.

What is MTN's role?
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 will submit 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 later this year. 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 at increased risk of HIV.

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Will the HOPE or DREAM open-label extension studies contribute to potential dapivirine ring approval?
IPM will be 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, however, IPM plans to 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.

When is a decision expected?
IPM is hopeful that the first regulatory approvals could be received late 2018. 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.

Why does it take so long?
The application that IPM will be submitting to regulatory authorities contains data from more than 250 laboratory and clinical studies, detailing nearly 15 years of research. The average length of an application is 500,000 pages, and regulators must review this information carefully. Because dapivirine is a new drug, the process may be more complex 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?
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 late 2018, 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. Because the dapivirine ring contains an ARV drug, regular HIV testing will be required; some countries may require a health worker to prescribe or dispense the product to women.

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 ring to be approximately 7 USD. As production is scaled up and manufacturing processes are optimized, costs could be reduced to as low as 2.50 USD a ring.

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 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 one 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. 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.

New studies and next steps

What is the REACH study?
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. REACH will also collect information on the safety of these approaches and assess whether biological or physiological factors affect product efficacy or HIV susceptibility. The study will involve approximately 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 at highest risk of 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 with sufficient adherence. 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. 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 their safety 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 completed a safety study of the ring (MTN-023 /IPM 030) among adolescent girls in the United States. The REACH study will contribute important information about the ring in African girls.

When will REACH start and be completed?
The study is expected to start late 2017, pending ethics committee and in-country approvals, and should take approximately three years to complete. Results are anticipated in 2020.

Are studies needed of the ring in pregnant and breastfeeding women?
Women need HIV prevention products that will be safe and effective to use in all stages of life, including during pregnancy and breastfeeding, when the risk of acquiring HIV from an infected partner may be particularly high. In the ASPIRE and The Ring Study Phase III trials of the dapivirine ring, women were required to use effective contraception because it was not known if or how dapivirine might affect a woman's pregnancy or the development of her fetus. Participants who became pregnant during the study, immediately stopped use of the ring. But if the ring is approved, its intended use will be for sexually active women ages 18-45 – women of reproductive age. Understanding its safety during pregnancy and breastfeeding will require carefully designed trials that are implemented with the highest ethical standards and regard for the safety and well-being of this special population.

Have studies been conducted or being planned of the dapivirine ring in breastfeeding and pregnant women?
As the first study of its kind involving the dapivirine ring, MTN-029/IPM 039 was designed to determine whether drug released from the ring into the vagina gets absorbed into breastmilk without exposing infants to dapivirine. The study enrolled 18 women who were no longer breastfeeding but still producing breast milk and who used the ring for 14 consecutive days. Its results are expected to be reported mid-2017. MTN is planning additional studies to be conducted in Africa. MTN-041, would explore attitudes of pregnant women and their male partners about ring and PrEP use during pregnancy; 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.

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What studies are being conducted of longer-acting and dual-purpose dapivirine 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. 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, researchers will assess safety of 14-day use 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, will evaluate 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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