

## QUESTIONS AND ANSWERS

### Dapivirine ring studies in adolescent girls and young women: MTN-023 /IPM 030 and the REACH Study

#### In a nutshell

- ▶ Adolescent girls and young women are especially vulnerable to acquiring HIV, particularly in regions like sub-Saharan Africa, where it is estimated that 1,000 young women ages 15-25 are infected every day.
- ▶ A monthly vaginal ring containing an antiretroviral (ARV) drug called dapivirine was safe and helped protect against HIV in two large trials. [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.
- ▶ Based on the results of ASPIRE and The Ring Study, and several supporting studies, IPM is seeking regulatory approval of the dapivirine ring for women ages 18-45. A decision could be received late 2018.
- ▶ Because regulatory authorities would need information about the safety of the ring in girls under age 18 to consider the ring's approval in this population, the MTN, in collaboration with the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), conducted a study of the ring in girls ages 15-17 in the United States. [Results of this study](#), MTN-023/IPM 030, found the ring both safe and acceptable to use.
- ▶ A second study, called [REACH](#), will provide additional information on the safety of the ring in young African women, as well as of oral pre-exposure prophylaxis (PrEP). REACH will also assess how young women use the monthly ring and daily PrEP and their preferences. The study is planning to enroll adolescent girls and young women ages 16-21 beginning early to mid-2018.



#### 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, dapivirine, instead, that is slowly released into the vagina during the month that it is used. The ring, which is made of a flexible material, sits high inside the vagina. Women can insert and replace it themselves.

Dapivirine, also known as TMC-120, belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors that block HIV's ability to replicate itself inside a healthy cell. IPM holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, part of the Janssen Pharmaceutical Companies of Johnson & Johnson, which is designed to ensure that women in low-resource settings have affordable access to any dapivirine-based vaginal HIV prevention method.

### Dapivirine ring studies in adolescent girls and young women

#### MTN-023 /IPM 030

##### 1. What was the aim of MTN-023 /IPM 030?

MTN-023/IPM 030 was a Phase IIa study that evaluated the safety and acceptability of the dapivirine vaginal ring among teenage girls ages 15 to 17 in the United States. The study was conducted while two Phase III efficacy trials of the ring – ASPIRE and The Ring Study – were underway among African women. The results of these efficacy trials would determine whether regulatory approval of the ring would be pursued for women ages 18-45. MTN-023/IPM 030 was designed to collect the kind of data that regulatory authorities would need to expand approval of the ring to also include girls under age 18.

## 2. Who conducted and funded the study?

MTN-023/IPM 030 was conducted through a collaboration between the Microbicide Trials Network (MTN) and the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). Both the MTN and the ATN are funded by the U.S. National Institutes of Health (NIH). The ATN is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The MTN is funded by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH) and NICHD. Kathleen E. Squires, M.D., of Thomas Jefferson University in Philadelphia, was protocol chair, and Katherine Bunge, M.D., of the University of Pittsburgh, was protocol co-chair. As the regulatory sponsor and license holder of the dapivirine ring, the International Partnership for Microbicides (IPM) provided both the placebo rings and the rings containing dapivirine for use in MTN-023/IPM 030.

## 3. When and where was MTN-023/IPM 030 conducted?

MTN-023/IPM 030 was conducted between July 2014 and July 2016 at six clinical research sites in the United States: two sites affiliated with the MTN (University of Pittsburgh and the University of Alabama at Birmingham) and four with the ATN (St. Jude Children's Research Hospital in Memphis; The Fenway Institute in Boston; Children's Hospital at Montefiore Medical Center, Bronx, N.Y.; and University of Colorado Denver School of Medicine).

## 4. How was MTN-023/IPM 030 designed?

MTN-023/IPM 030 enrolled 96 young women between 15 and 17 years old who had experienced sexual intercourse at least once. Participants were randomly assigned in a 3:1 ratio to use either the dapivirine vaginal ring or a placebo ring that looked the same but contained no active drug, with 73 participants assigned to use the dapivirine ring and 23 participants, to use the placebo. Participants learned how to insert and remove the ring when they first enrolled and received additional guidance as needed at monthly follow-up visits. They were also taught how to reinsert the ring should it come out accidentally. Because the study was "blinded," neither participants nor researchers knew who was in which group during the study.

Samples of blood, urine and vaginal fluid were collected at each monthly clinic visit so that researchers could monitor participants' health. Researchers also looked at blood and vaginal fluid to assess how much drug from the ring was absorbed in the body. Participants were asked questions about their use of the ring, including whether they were able to keep it in place during the previous month. Objective measures of adherence to ring use included drug levels in plasma samples and analysis of used rings that were returned to the clinic after each month.

At five of the six study sites, 21 participants took part in an in-depth interview at the end of the study to better understand their experiences using the vaginal ring.

## 5. What are the results of the MTN-023/IPM 030 study?

The study found no differences in safety outcomes between the dapivirine ring and the placebo ring. Adherence to ring use was also high. By self-report, 42 percent of participants said they had never removed the ring except to replace it monthly. In the dapivirine group, 87 percent of plasma samples had detectable levels of drug suggestive of the ring being used the previous day; 95 percent of the rings returned after use had drug levels that suggested regular use during the previous month. Questions asked of participants three months into the study and after six months indicated the ring was highly acceptable, with 95 percent saying it was easy to use and 74 percent indicating they were not aware of the ring during daily activities. Some were worried that their partner would feel it during sex, but overall, the majority of participants (93 percent) said they liked the ring. Results were reported at the 9<sup>th</sup> IAS Conference on HIV Science ([IAS 2017](#)) in Paris.

## 6. How are these results important?

The dapivirine ring was shown to be both safe and help protect against HIV in the ASPIRE and The Ring Study Phase III trials, which together, enrolled more than 4,500 women ages 18-45 from four African countries. IPM is seeking regulatory approval of the ring for adult women of the same age, based on the results of these trials and several supporting studies. If approved, the dapivirine ring would be the first biomedical prevention product exclusively for women. MTN-023/IPM 030 provides the kind of information that regulatory authorities would need to consider expanding approval of the ring to also include girls under age 18. Finding the ring safe and well

tolerated by U.S. adolescent girls, MTN researchers are now planning a second study, called REACH, that will collect safety data among adolescent girls and young women in Africa, who are among the most vulnerable population at risk of acquiring HIV. (See *REACH QA below*.)

#### **7. What was done to protect the safety of study participants?**

As with all NIH-funded studies, MTN-023/IPM 030 incorporated a multi-tiered safety review process, beginning at the site level, that includes strict national and international standards and procedures for monitoring and reporting, intended to protect the safety and well-being of participants. Potential volunteers were carefully screened by study staff to ensure that only those for whom it would be safe to participate could enroll. For instance, because it was not known if or how dapivirine might affect pregnancy, participants were required to use an effective method of birth control during the study, even if they were not currently sexually active.

#### **8. What kind of approvals were required to conduct this study?**

MTN-023/IPM 030 underwent extensive and rigorous reviews by the NIH, the U.S. Food and Drug Administration and each site's Institutional Review Board (IRB). Local IRBs ensure that studies are scientifically valid and ethically conducted and provide oversight for the duration of the trial. In addition, each trial site had a community advisory board that provides input to research teams prior to and during a trial.

#### **9. Did participants in MTN-023/IPM 030 provide informed consent?**

Because both the dapivirine ring was an investigational product and participants were minors, permission of a parent or legal guardian was required along with the participant's assent. (Emancipated minors could provide independent informed consent if state laws and regulations allowed.) Prior to screening, again at enrollment, and throughout the duration of the study, participants, as well as their parents or guardians, were educated about all study procedures, any possible risks, benefits and alternatives to participation as well as the study's time requirements. Study staff also explained that participants did not have to take part in the study and could leave it at any time, without consequence.

## **The REACH Study**

#### **1. 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 pre-exposure prophylaxis (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.

#### **2. Who is conducting and funding the study?**

The REACH study is being conducted by the MTN, and as such, is funded by the NIH institutes that support MTN: NIAID, NICHD and NIMH. Lulu Nair, MBChB, MPH, of the Desmond Tutu HIV Foundation in South Africa is protocol chair, with Connie Celum, MD., MPH (University of Washington, USA) and Kenneth Ngunjiri, PhD, (Jomo Kenyatta University of Agriculture and Technology, Kenya) serving as co-chairs.

#### **3. Where will REACH be conducted?**

REACH will be conducted at five sites in four countries: in Kenya, at the Kenya Medical Research Institute (KEMRI) in Kisumu; in Uganda, at the Makerere University-Johns Hopkins University (MU-JHU) clinical research site; in South Africa, at both the Wits Reproductive Health and HIV Institute (Wits RHI) in Johannesburg and the Emavundleni site of the Desmond Tutu HIV Foundation (DTHF), Cape Town; and in Zimbabwe, at the Spilhaus clinical research site, University of Zimbabwe College of Health Sciences, Harare.

#### **4. When is REACH expected to start, and to be completed?**

The study is expected to start by mid-2018, pending ethics committee and in-country approvals, and should take approximately three years to complete. Results are anticipated in 2020.

## 5. What kind of approvals are required to conduct this study?

The study has undergone rigorous reviews by NIH and the FDA and is in the process of undergoing similar reviews by each site's Institutional Review Board (IRB) and/or Ethics Committee (EC). Local IRBs and ECs ensure that studies are scientifically valid and ethically conducted and provide oversight for the duration of the trial. In addition, each trial site has a local youth community advisory board that has provided and will continue to provide input to the research team prior to and during the trial.

## 6. Will participants provide informed consent?

The legal age at which an individual may provide informed consent to enroll in a research study is 18. For those under age 18, parental consent and the assent (agreement) of the minor is required. The exception applies for mature or emancipated minors, who although under the age of 18, are, for example, already married, a mother or head of a household.

## 7. How is REACH designed?

REACH is a type of clinical trial called an open-label study. Open-label studies do not have a placebo group – all participants use an active product. In REACH, there are two products: the dapivirine vaginal ring, which is used for a month at a time, and an oral tablet called Truvada taken daily, a regimen often referred to as PrEP. All participants will use each product for six months. Random assignment will determine whether PrEP is used for the first six months and then the ring for the following six months, or the ring first and then PrEP. After experiencing both approaches, participants will have a choice of using either the ring or PrEP – or neither – for an additional six months.

To evaluate the safety of each approach, researchers will conduct medical exams and do laboratory tests of blood, urine and vaginal fluid.

To evaluate adherence to and acceptability of PrEP and the vaginal ring, participants will answer questions about their use and experience with each product both on a computer and in face-to-face conversations with site staff. In-depth interviews and focus group discussions will also help understand what motivates or is challenging about using each product; whether they experience stigma; how relationships with family, friends and male partners may impact product use; and their preferences for either PrEP or the ring, or both. Objective measures of adherence will also help to evaluate how well participants are using each approach. PrEP use will be measured by drug levels in blood samples taken at each monthly visit. For the ring, researchers will look at the amount of residual drug left over in used rings returned each month. Individual adherence results will be shared with participants periodically during the study to help to help facilitate discussion about adherence and how it relates to protection.

## 8. Why is a study like REACH needed?

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 regularly. Researchers need to understand the challenges young women face in using these products so strategies can be identified that can help. Even so, for PrEP and the dapivirine ring to be made available to girls under the age of 18, national regulatory bodies need to be assured of their safety in this population. To date, there is very little safety data on 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 age 15-17 in the United States, which found the ring both safe and acceptable to use. The REACH study will add to this data by contributing important information about the ring in African girls.

## 9. What were the results of ASPIRE and The Ring Study?

Primary results of both ASPIRE and The Ring Study were reported in February 2016. Overall, the two studies, which involved more than 4,500 women from four African countries 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, which

Was also associated with older age. The ring reduced HIV risk by 56 percent in women 22 and older in ASPIRE, while in those 18-21, the ring was not effective. 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 – across all age groups – was at least 56 percent and as high as 75 percent or more with near perfect use. The same exploratory analysis suggested an 84 percent reduction in risk among younger women who were able to use the ring consistently.

#### **10. Is regulatory approval of the dapivirine ring being sought?**

Yes. 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) 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.

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

Daily use of an ARV tablet called Truvada (PrEP) is an approach now approved in many countries, including South Africa, Kenya and Zimbabwe, and recommended by the 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. 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 – 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 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.

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More information about the dapivirine ring is available at [www.mtnstopshiv.org/news/studies/mtn025](http://www.mtnstopshiv.org/news/studies/mtn025) , [www.mtnstopshiv.org/news/studies/mtn020](http://www.mtnstopshiv.org/news/studies/mtn020) and [www.ipmglobal.org](http://www.ipmglobal.org).

#### **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>.*