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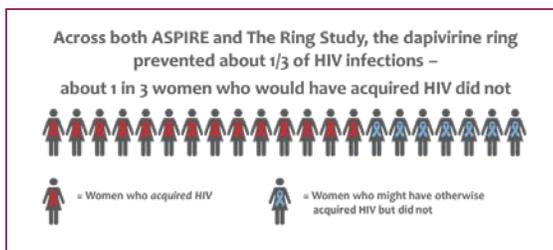
## After ASPIRE: HOPE and other MTN Studies of the Dapivirine Ring



### Overview

The dapivirine vaginal ring is the first HIV prevention product developed specifically for women that has been found to be safe and to help protect against HIV in two independently conducted large-scale trials. [ASPIRE](#) and [The Ring Study](#) involved 4,588 women in four African countries where HIV rates for women continue to be among the highest globally. Across both studies, HIV risk was reduced by about one-third, meaning that one in three women who might have acquired HIV did not. Higher levels of protection were seen in women who used the ring most regularly.

Vaginal rings are flexible products that fit high up inside the vagina where they release a medication slowly over time. The ring tested in these two trials contains an antiretroviral (ARV) drug, dapivirine, as a way to offer women potentially longer-acting protection against HIV. The ring is used for a month at a time, and women can insert and remove the ring themselves. The dapivirine ring was developed by the International Partnership for Microbicides (IPM), a non-profit organization based in South Africa and the United States. IPM is also the ring's regulatory sponsor.



The primary results of both studies were reported at the [Conference on Retroviruses and Opportunistic Infections \(CROI\)](#) in February 2016, when ASPIRE results also were published online in the [New England Journal of Medicine](#). ASPIRE found HIV risk was cut by more than half in women older than 21; for women ages 18-21, who as a group appeared to use the ring least consistently, the ring was not effective. Similar results were seen in The Ring Study.

[New results](#) reported by ASPIRE researchers at The International Conference on AIDS ([AIDS 2016](#)) in Durban suggest higher levels of protection can be achieved with regular and consistent use, finding that among women who appeared to use the ring most or all of the time, HIV risk was cut by at least more than half, and in some analyses, by 75 percent or more.

ASPIRE, also known as MTN-020, was conducted by the [Microbicide Trials Network](#) (MTN), an HIV/AIDS clinical trials network 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 of the U.S. National Institutes of Health (NIH). The Ring Study, also known as IPM 027, is being conducted by IPM.

Because at least two Phase III efficacy trials are typically needed for a product to be considered for regulatory approval, ASPIRE and The Ring Study were conducted in parallel to accelerate the timeline to the ring's potential approval. Data from ASPIRE and The Ring Study, and from several smaller supporting studies, will now be compiled into a comprehensive packet of information that IPM expects to submit to regulators in 2017.

In the meantime, former participants of each study will be provided the opportunity to use the dapivirine ring in the context of open-label extension (OLE) trials – [HOPE](#) for former ASPIRE participants, and DREAM for former participants of The Ring Study. As research studies, both OLEs will collect additional information about adherence and safety of the dapivirine ring.

Other MTN studies are under way or being planned to help address questions that a Phase III trial cannot, such as whether the ring is safe to use during pregnancy and breastfeeding; and to address what can be done to curb the alarming rate of HIV infections in younger African women, in whom the ring was not effective in either ASPIRE or The Ring Study. These studies include:

- **MTN-032** looks to better understand women’s use of the dapivirine ring in both ASPIRE and HOPE and if and how adherence patterns differ between ASPIRE, a placebo-controlled trial, and the HOPE open-label extension trial in which all women are offered the dapivirine ring, yet may choose not to accept it.
- **MTN-034/IPM-045** looks to address the HIV prevention needs of adolescent girls and young women in a design that will evaluate both the monthly dapivirine ring and daily use of Truvada as oral pre-exposure prophylaxis (PrEP). The study will also examine whether certain biological or physiological factors affect how the active drugs are taken up in the body.
- **MTN-029/IPM 039** is assessing whether dapivirine released from the vaginal ring gets into breastmilk. It’s the first step in determining whether the ring is safe to use during pregnancy and breastfeeding, when women are at particular risk of acquiring HIV.

*These studies, as well as HOPE, are described in more detail in the following pages.*

### **ASPIRE Results Recap**

ASPIRE– A Study to Prevent Infection with a Ring for Extended Use, or MTN-020, enrolled 2,629 sexually active HIV-negative women ages 18-45, and was conducted between August 2012 and June 2015 at 15 NIAID-funded clinical research sites in Malawi, Uganda, South Africa and Zimbabwe. Jared Baeten, M.D., Ph.D., of the University of Washington, and Thesla Palanee-Phillips, Ph.D., M.Sc., of the Wits Reproductive Health and HIV Institute, South Africa, led the study.

Women who enrolled in the study were randomly assigned to either use the dapivirine ring or a placebo ring that looked the same but contained no active drug, and they learned how to insert and remove the ring themselves. Women received a new ring at each monthly visit, plus condoms, HIV prevention counseling and diagnosis and treatment of sexually transmitted infections (STIs). Participation averaged 18 months; some women were in the study for close to three years.

To arrive at their results, researchers compared the number of HIV infections and the number and types of side effects that occurred among women using the dapivirine ring with those in the placebo group:

- ▶ The dapivirine ring reduced the risk of HIV by 27 percent overall – there were 27 percent fewer women who acquired HIV in the group assigned to use the dapivirine ring than in the placebo ring group. (Of 168 women who acquired HIV, 97 were in the placebo group and 71 were in the dapivirine ring group.)
- ▶ There was a 37 percent reduction in HIV infections in a second analysis planned early in the study that excluded data from two sites with less than ideal retention and adherence.
- ▶ HIV risk was reduced significantly more among the study’s older participants, who also appeared to use the ring most consistently. Women 25 and older in the dapivirine ring group were 61 percent less likely to acquire HIV than women of the same age in the placebo group. Further analyses found the lack of protection was confined to those ages 18 to 21, but for women older than 21, HIV risk was cut by 56 percent.
- ▶ Additional analyses were conducted of used rings to explore the degree of HIV protection associated with consistent use. [Results](#), presented at AIDS 2016, found the level of HIV protection for those who appeared to use the ring most consistently was as high as 75 percent or more.
- ▶ There were no safety concerns associated with the dapivirine ring, and among women who acquired HIV, no differences in the number or type of drug resistance cases between the dapivirine and placebo groups.

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## **HOPE: HIV Open-label Prevention Extension study**

HOPE (HIV Open-label Prevention Extension, or MTN-025) is designed to provide former ASPIRE participants the opportunity to use the dapivirine ring in the context of a study. At the same time, women may enroll in HOPE even if they do not wish to use the ring.

**As a research study, HOPE will build on the results of ASPIRE by gathering 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 protection. HOPE will also seek to understand the reasons why some participants who took part in ASPIRE choose not to enroll in HOPE, and why some women who choose to enroll in HOPE do not want to use the ring. By including all-comers, researchers hope to better understand why the ring may work well as an HIV prevention strategy for some women but not for others, how this might change over time or in different circumstances, and what factors influence women’s decisions about the ring.**

HOPE will be conducted very differently from a Phase III clinical trial. For example, there is no randomization and no placebo ring. All women, if they choose, receive the dapivirine ring. Other features of its design are meant to be taken as first steps in the transition toward a more “real world” delivery model.

- Visits will be monthly for the first three months, and then be quarterly thereafter to get closer to how the ring might be delivered in public health settings. At quarterly visits, women will be able to obtain three rings for monthly use over the next three months, or they may return to the clinic each month for a new ring. HIV testing and services offered by the study will be available only at quarterly visits, unless a participant has special concerns that require more immediate attention.
- While staff will counsel participants on the importance of adherence, communication will necessarily need to strike a balance between providing encouragement on the one hand and empowering women to make their own choices on the other. Site staff want participants to feel comfortable with making their own decisions and also to be open about the reasons they may or may not want to or be able to use the ring.

In ASPIRE, participants were using a vaginal ring for the first time and had no knowledge of its efficacy or long-term safety. Researchers are hopeful that in knowing the results of both ASPIRE and The Ring Study, women will feel more at ease about the ring and motivated to use it as consistently as possible. In other OLEs that followed Phase III trials of oral pre-exposure prophylaxis (PrEP), adherence to product use increased, and as a result, those studies were able to demonstrate the approach was more effective than was seen in the Phase III trials. The iPrEx study, for instance, found oral Truvada reduced the risk of HIV by 42 percent among men who have sex with men (MSM), with evidence that only about half of the participants adhered to the daily regimen, while in the open-label PROUD and IPERGAY studies of MSM, adherence was nearly 100 percent and PrEP was found to be 86 percent effective in both trials. Whether the same will be true with the ring in HOPE remains to be seen.

The first of HOPE’s trial sites opened mid-July 2016, with the remaining sites expected to open in the coming months as in-country approvals are received. Women will be able to stay in HOPE for about a year after they enroll. The study is expected to be completed by early 2018, with results expected later that year, within the same timeframe that the first regulatory approvals for the dapivirine ring, if granted, could be expected.



HOPE is being led by Jared Baeten, M.D., Ph.D., of the University of Washington, Thesla Palanee-Phillips, Ph.D., M.Sc., of the Wits Reproductive Health and HIV Institute, South Africa, and Nyaradzo Mgodzi, MBChB, MMed, from the University of Zimbabwe-University of California San Francisco in Harare, Zimbabwe.

### **MTN-032: Understanding women's adherence in ASPIRE and HOPE**

Why women did or did not use the ring in ASPIRE, or why they did not use it all the time, are questions that MTN-032 seeks to answer among a cross-section of former ASPIRE participants. MTN-032 will also help determine if and how women's interest in and ability to use the ring differs within the context of the HOPE open-label access study. 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.

MTN-032 aims to understand the social, cultural or trial-specific factors that may have impacted women's intentions to use the dapivirine ring and their actual and reported ring use. For instance, did women feel compelled to insert the ring just before a study visit to please investigators, only to remove it afterward? And if so, why? In addition, MTN-032 will explore participants' views of various adherence support interventions and participant engagement activities employed at different sites during ASPIRE, and their understanding of ASPIRE results and whether or not this influences their interest in and/or ability to join HOPE and to use the dapivirine vaginal ring being offered to them.

MTN-032 will complement and expand on the qualitative and quantitative data collection component of both ASPIRE and HOPE.

MTN-032 will involve two phases:

- Phase I will involve up to 224 former ASPIRE participants who had been assigned to use the dapivirine ring and whose blood tests and returned rings suggest consistently high ring use, consistently low ring use or inconsistent use of the ring during ASPIRE. Participants will receive their individual test results in private and then be asked if they would be willing to talk about their experience with a trained interviewer in either a one-time in-depth interview or a focus-group discussion, which would be determined by randomization. To allow for more open discussion about age-specific adherence challenges, separate focus groups will take place, with one including younger women – those who were ages 18 -21 when they enrolled in ASPIRE, and the other consisting of women who were ages 22 - 45 at enrollment.
- Among those Phase I participants who opt to enroll in HOPE, approximately 84 will take part in Phase 2 of MTN-032, which involves a single in-depth interview. Researchers will be looking to understand the reasons women with varying levels of adherence in ASPIRE decide to enroll into HOPE, whether they choose to accept the ring and if and how knowing the ring's efficacy has any bearing on both their intended and actual use. Women's views related to ring uptake, marketing and product roll-out will also be solicited.

MTN-032 is being conducted at six of the 15 clinical research sites (CRSs) for ASPIRE and HOPE: UNC Lilongwe Clinical Research Site in Malawi; the Makerere University-Johns Hopkins University Research Collaboration CRS in Kampala, Uganda; the South African Medical Research Council (SAMRC) Botha's Hill CRS in KwaZulu-Natal; Wits Reproductive Health and HIV Institute (Wits RHI) CRS in Johannesburg, South Africa; and two CRSs affiliated with the University of Zimbabwe-University of California San Francisco (UZ-UCSF) in Harare and Chitungwiza.

Leading the study are Elizabeth Montgomery, Ph.D., of RTI International/Women's Global Health Imperative (WGHI) program in San Francisco, together with Sarita Naidoo, Ph.D., HIV Prevention Research Unit, SAMRC, South Africa; and Jonathan Stadler, Ph.D., of Wits RHI.

The study began in June 2016. Phase 1 is expected to be completed by early 2017; Phase 2 will be conducted after HOPE has concluded in 2018, with results of both phases of the study expected by mid-2019.

### **MTN-034 / IPM 045 – Meeting the HIV prevention needs of adolescent girls and young women**

MTN-034/IPM 045 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, MTN-034/IPM 045 will evaluate how adolescent girls and young women use the monthly dapivirine vaginal ring and Truvada<sup>®</sup> as daily PrEP, and their preferences for either or both approaches. The study will also collect much needed information on the safety of these approaches in young women and assess whether biological or physiological factors affect how the active drug in each of these products is taken up in the body or may contribute to HIV susceptibility. The study, which is expected to launch early 2017, will enroll approximately 300 girls and young women ages 16-21 at five trial sites in Kenya, South Africa and Zimbabwe. All participants will use the ring and oral PrEP, each for six months. (There will be no placebo ring or placebo tablet.) After experiencing both approaches, participants will have a choice of using either the ring or PrEP –or nothing at all – for an additional six months. The study is expected to take about three years to conduct.

The World Health Organization has recommended oral PrEP for all persons at substantial HIV risk, defined as populations with 3 percent or higher HIV incidence, which includes young African women in some settings. A number of countries, including South Africa and Kenya, have approved Truvada as PrEP and are making plans for its introduction. While adolescent girls and young women stand to benefit from PrEP, and potentially from the dapivirine ring, should it eventually receive regulatory approval, neither can be effective if not used with sufficient adherence. Indeed, studies have shown adherence to be particularly challenging for younger women. In VOICE, women under age 25 were the least likely to use their assigned products – including oral Truvada – and the most likely to acquire HIV. In ASPIRE, the dapivirine ring was not effective in women ages 18-21, who used the ring least consistently. As these were Phase III trials, participants did not know whether or not they were using a placebo or whether the study product was safe or effective. In contrast, in ADAPT (HPTN-067), an open-label PrEP study involving women in Cape Town, South Africa –adherence to daily PrEP was high (approximately 80 percent based on blood drug levels), even among those under 25.

Similarly, MTN-034 will help determine whether adolescent girls and young women are more apt to use the dapivirine ring and oral PrEP in the context of an open-label study, and whether when given a choice of products, adherence improves. MTN-034 will also look at the safety of these products in this population. This is especially important for the dapivirine ring. While IPM, the ring's developer, plans to seek regulatory approval for use of the dapivirine ring by women ages 18-45 based on results of ASPIRE and The Ring Study and several smaller studies, data specifically on the ring's safety and use among women younger than 18 would be required if the ring is to be made available to this population.

MTN-034 will be led by Gonasagrie Nair, MBChB, of the Desmond Tutu HIV Centre in Cape Town; Kenneth Ngunjiri, M.P.H., Ph.D., Department of Public Health, Jomo Kenyatta University, Nairobi, Kenya, and Connie Celum, M.D., M.P.H., University of Washington, Seattle.

### **MTN-029 /IPM 039 – A study of the dapivirine ring in lactating women**

The MTN has long recognized that women need 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. Included in its scientific portfolio is a comprehensive research program purposefully designed to take incremental steps in determining whether HIV prevention products are safe and effective in protecting women against HIV infection during all stages of pregnancy and motherhood.

MTN-029/IPM 039, which is the first study of its kind involving the dapivirine vaginal ring, will determine whether drug released from the ring into the vagina gets absorbed by breastmilk. Approximately 16 women who are no longer breastfeeding but still producing breast milk will be enrolled and use the ring for 14 consecutive days. The study is designed so that important information can be collected without exposing infants to dapivirine. Its results may support future studies involving breastfeeding mothers and their infants. The study began in March 2016 and is being conducted at the University of Pittsburgh and the University of Alabama Birmingham. Leading the study are Lisa Noguchi, Ph.D., CNM, Johns Hopkins University Department of Epidemiology, and Richard Beigi, M.D., M.Sc., Magee-Womens Hospital of the University of Pittsburgh Medical Center. Results are anticipated in 2017.

### ***About the dapivirine vaginal ring***

The dapivirine ring is made of flexible silicone and measures 56mm (about 2 ¼ inches) in diameter and 7.7mm thick (3/8 inch). Each ring contains 25mg of the ARV dapivirine.

Dapivirine, also known as TMC-120, belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTIs) that block the ability of HIV to multiply inside healthy cells. NNRTIs are used successfully in the treatment of HIV and to prevent mother-to-child transmission. Dapivirine was originally developed by Janssen Sciences Ireland UC for use in the treatment of HIV. IPM began developing dapivirine as a microbicide for HIV prevention in 2004 when Janssen granted it a royalty-free license, which expanded to an exclusive worldwide rights agreement in 2014. Studies have shown that the ring can deliver dapivirine to vaginal tissue for a month or longer with low absorption elsewhere in the body. Data from more than 250 clinical and laboratory studies, many of which were conducted in Europe and the United States, will be included in IPM's regulatory submission for the dapivirine ring's approval. Studies conducted by the MTN include MTN-024/IPM 031 looking at the ring's safety and drug absorption in post-menopausal women and a similar study in adolescent girls, MTN-023/IPM 030, which was conducted in collaboration with the Adolescent Trials Network for HIV/AIDS Interventions.

Although not part of the regulatory dossier, the MTN, in partnership with IPM, will be conducting an early phase study (MTN-030/IPM 041) of a ring containing both dapivirine and the hormonal contraceptive levonorgestrel, a product IPM is developing to provide women protection against both HIV and unplanned pregnancy.

### ***Why consider a vaginal ring for HIV prevention?***

Although the World Health Organization has recommended that PrEP be offered to all persons at substantial HIV risk, and a number of countries, including South Africa and Kenya, have approved Truvada as PrEP. It is only one option. The vaginal ring, if approved, could be another.

Some women may find a vaginal ring that they replace once a month more suitable and easier to use consistently than say, taking a daily ARV tablet as oral PrEP. While for other women, a vaginal ring may *not* be the desired approach and instead they may prefer daily or on-demand products. What's important is that women have choices when it comes to protecting themselves against HIV – whether it be oral PrEP, a vaginal ring or any other intervention – because only when a product is used will it be effective.

Women account for 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual intercourse is the primary contributor to the region's heavy HIV burden. Despite advances in preventing HIV, women – young women, especially – still face disproportionate risk, and effective prevention options, including oral PrEP, may not be accessible to or practical for many women.

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More information and materials about ASPIRE, HOPE and MTN studies of the dapivirine ring are available at <http://www.mtnstopshiv.org/news/studies/mtn020> and <http://www.mtnstopshiv.org/news/studies>

More information about the dapivirine ring, The Ring Study and the DREAM open-label extension study can be found at [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 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>.*