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QUESTIONS AND ANSWERS

ASPIRE – A Study to Prevent Infection with a Ring for Extended Use

The Big Picture

1. What is the aim of ASPIRE?

ASPIRE – A Study to Prevent Infection with a Ring for Extended Use, also known as MTN-020, is a Phase III clinical trial that seeks to determine whether a woman's use of a vaginal ring containing the antiretroviral (ARV) drug dapivirine is a safe and effective method for protecting against HIV when used for a month at a time. The study, which enrolled 2,629 HIV-negative women at 15 clinical research sites in Malawi, Uganda, South Africa and Zimbabwe, will also help determine whether study participants find the ring practical and easy to use within the context of their daily lives. The dapivirine ring was developed by the International Partnership for Microbicides (IPM), which is conducting a second Phase III trial called The Ring Study. ASPIRE and The Ring Study are both the first effectiveness trials of a vaginal ring for HIV prevention – a method that could feasibly offer women long-acting, discreet protection against HIV – and of an ARV-based HIV prevention product using a drug other than tenofovir or a tenofovir combination. As sister studies, ASPIRE and The Ring Study are designed to provide the strength of evidence to support potential licensure of the dapivirine vaginal ring for preventing HIV in women.


Andrew Loxely

2. Who is conducting and funding the study?

ASPIRE is a study of 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). Jared Baeten, M.D., Ph.D., of the University of Washington, U.S., is protocol chair; and Thesla Palanee, Ph.D., of the Wits Reproductive Health and HIV Institute, South Africa, is protocol co-chair. As the regulatory sponsor and license holder of the dapivirine ring, IPM provided both the placebo rings and the rings containing dapivirine for use in ASPIRE.

3. What is the status of ASPIRE?

ASPIRE began in August 2012 and enrolled 2,629 HIV-negative women at 15 clinical research sites in Malawi, Uganda, South Africa and Zimbabwe. Follow-up of all study participants was completed late June 2015. Women in ASPIRE used their assigned product (placebo ring or a dapivirine ring) for at least one year, although those who enrolled earlier in the study had used their assigned ring for up to 34 months at the time they exited the study. Results of ASPIRE are expected to be reported early 2016, when IPM researchers anticipate efficacy and preliminary safety results from The Ring Study will also be available.

4. What is The Ring Study, and why the need for two trials of the dapivirine ring?

The Ring Study, also known as IPM 027, began in April 2012 and has since enrolled 1,959 HIV-negative women at seven research centers – six in South Africa and one in Uganda. Unlike ASPIRE, women enrolled in The Ring Study were asked to remain in the study for two years because one of the study's main objectives is to evaluate the long-term safety of the ring. Moreover, for every woman using a placebo ring there are two women who use the dapivirine ring. The study is scheduled to conclude at the end of 2016, after the last participants have used their ring for two years, though efficacy and preliminary safety results of The Ring Study are expected early 2016.

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Results from at least two Phase III efficacy trials are usually needed for a product to be considered for regulatory approval. This is why ASPIRE and The Ring Study, which together involve more than 4,500 women in southern and eastern Africa, were designed to take place concurrently – so that the timeline to potential approval and product access would be as short as possible. Pending results of ASPIRE and The Ring Study, and several supporting studies, IPM, as the ring's developer and regulatory sponsor, will seek regulatory approval of the ring and collaborate with key partners to help ensure the ring is made available to women in developing countries at low cost and as soon as possible. This is important given women's urgent need for new HIV prevention tools they are able and willing to use. Of the more than 35.3 million people living with HIV, more than half are women. Women account for nearly 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual sex is the primary driver of the epidemic. Young women are especially vulnerable — women ages 15 to 24 are twice as likely as young men to be infected with HIV. Efforts to promote abstinence, monogamy and the use of male condoms have not been enough to stop the HIV epidemic nor are these practical methods in many settings.

5. Why consider a vaginal ring for preventing HIV?

Vaginal rings are flexible products that fit comfortably high inside the vagina and provide slow, controlled delivery of drugs over a period of time. Women in many countries already use vaginal rings that are designed to deliver contraceptive hormones. IPM's dapivirine ring adapts this commonly used medical technology by using an ARV instead of contraception to offer women potentially long-acting protection from acquiring HIV through sex with an infected male partner. Because women only need to replace the ring once a month, it may be an approach that some women find more suitable and easier to use consistently than, say, a vaginal gel used daily or at the time of sex, or taking a daily ARV tablet. Indeed, trials of these approaches have demonstrated that no matter how effective a product may be, it cannot offer protection if it is not used. Another potential advantage of a vaginal ring is the possibility of being able to combine both contraception and HIV prevention in one product. In fact, research on dual-purpose rings is already underway.

6. Is there a need for more than one HIV prevention approach?

Yes, because what's appealing to one group of people isn't necessarily going to be the case for others. Several studies have now shown that daily use of the ARV tablet Truvada is very effective for preventing HIV. Yet two studies, VOICE and FEM-PrEP, also indicated that for younger high-risk women in Africa, taking ARV tablets may not be the right approach. Similarly, VOICE and the FACTS 001 trial suggest that a vaginal gel – used daily or at the time of sex – didn't work for the young women in those studies. At the same time, results of the HPTN-067 (ADAPT) study looking at daily use of Truvada found that most of the women enrolled at the Cape Town, South Africa trial site were able to follow the daily regimen. According to tests of drug in blood samples, adherence was 93 percent at 10 weeks and 79 percent at 30 weeks. While results of studies may differ, what is clear is that different kinds of products, whether tablets, gels, rings, fast-dissolving films or long-acting injections, will appeal to different women at different times of their lives, with the one that best suits individual needs or lifestyles more likely to be used. This is why it is important to investigate different and complementary HIV prevention strategies.

7. What is the dapivirine vaginal ring?

The dapivirine ring is made of a flexible silicone material that measures 56mm (about 2 ¼ inches) in diameter and 7.7mm thick (3/8 inch). Each ring contains 25mg of the ARV dapivirine. When placed inside the vagina, the ring slowly releases the drug over time. The dapivirine ring is designed to be replaced every four weeks.

8. What is dapivirine?

Dapivirine, also known as TMC-120, is a type of ARV called a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs bind to and disable HIV's reverse transcriptase enzyme, a protein that HIV needs to make copies of itself. Different NNRTIs are used in the treatment of HIV and also for prevention of mother-to-child transmission. Dapivirine was initially being developed as an oral therapeutic agent to be used for treating HIV, but because of its favorable safety profile and physical and chemical properties it was decided that dapivirine was better suited for development as a microbicide for HIV prevention. As such, in 2004, IPM, a non-profit product development partnership based in Silver Spring, Md., received a royalty-free license to develop dapivirine for use as a microbicide in developing countries through an agreement with Janssen Science Ireland UC, a Janssen pharmaceutical company

of Johnson & Johnson. That license has since expanded to a worldwide rights agreement. To date, 17 studies have found dapivirine well tolerated and acceptable when formulated as a vaginal gel or ring. Studies of the dapivirine ring have also shown that high concentrations of active drug are delivered to vaginal tissue for a month or longer, with only trace amounts of drug being absorbed elsewhere in the body.

9. How is ASPIRE designed?
ASPIRE is a Phase III trial designed to evaluate the safety and effectiveness of the dapivirine vaginal ring for preventing the sexual transmission of HIV in women. Participants were randomly assigned to use either the dapivirine ring or a placebo ring (that looked the same but had no active drug) throughout the study, which for all women was at least one year. Participants received a new ring every four weeks at their monthly clinic visit. As part of the study, all participants received ongoing HIV risk reduction counseling, condoms and diagnosis and treatment of sexually transmitted infections (STIs).

In addition to determining the ring's safety and effectiveness, ASPIRE was designed to assess women's adherence to and acceptability of the ring. Other aims include looking to see whether different levels of drug in cells and tissue are associated with greater protection, as well as the nature and frequency of HIV drug resistance among those women who, despite the HIV prevention measures provided to all participants, acquired HIV during the study.

10. Will ASPIRE participants have access to the dapivirine ring if it's found safe and effective in ASPIRE?
A core principle of ethical conduct of biomedical HIV prevention research is the provision of access to proven products in the immediate post-trial period. Plans are underway for an open-label extension trial called HOPE (HIV Open-label Prevention Extension), or MTN-025, in which former participants would be able to use the dapivirine ring for approximately one year. Whether that study moves forward will depend on the outcome of ASPIRE. As a research study, HOPE would gather additional data on the safety of and adherence to the ring, information that would help understand issues important for broader implementation of the ring should it receive regulatory approval.

11. What are plans for regulatory approval of the dapivirine ring?
If ASPIRE and The Ring Study find the dapivirine ring safe and effective, IPM, as the organization that developed the dapivirine ring and the regulatory sponsor of the Phase III program for the product, will seek regulatory approval and licensure of the ring. In addition to results of ASPIRE and The Ring Study, the results of several other studies of the dapivirine ring will be included in a comprehensive dossier detailing more than 13 years of investigation. Among these are studies conducted by MTN at U.S. clinical research sites. MTN-024/IPM 031 looked at the ring's safety and drug absorption in post-menopausal women. A similar study in adolescent girls, MTN-023/IPM 030, is being conducted in collaboration with the Adolescent Trials Network for HIV/AIDS Interventions. Among IPM's completed or ongoing studies are those looking at condom functionality, possible drug interactions and effects of menses and tampon use.

IPM intends to seek product approval from the European Medicines Agency, the U.S. Food and Drug Administration (FDA) and the South African Medicines Control Council (MCC). IPM will also apply for World Health Organization (WHO) pre-qualification, a process in which WHO determines that a new drug or product meets global standards for quality, safety and efficacy. This is important, because drug regulatory authorities (NRAs) in developing countries decide which new products to approve based on WHO prequalification, as well as their review of EMA and FDA decisions. The earliest that a regulatory decision could be expected is late 2017 or early 2018 – about one year from the time of submission.

At the Trial Site

12. What approvals were needed to conduct the study?
ASPIRE underwent extensive and rigorous review by NIAID and the U.S. FDA. Moreover, before any site could begin the study, approvals were required of government and 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.

13. Who could participate in ASPIRE?
Women between the ages of 18 and 45 who were sexually active and HIV-negative at screening and enrollment were eligible to participate in ASPIRE, provided they met other study inclusion criteria. For instance, women who were pregnant or breastfeeding, or intended on getting pregnant, could not participate in ASPIRE.

14. Did women participating in ASPIRE provide informed consent?
Yes. Women who volunteered to join ASPIRE were educated 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. This process is called "informed consent" and it occurred prior to screening, again at enrollment, and throughout the study. Information was provided in simple terms and translated into local languages.

15. Were women taught how to insert and remove the ring?
Participants learned how to insert and remove the ring when they first enrolled into the study and received additional guidance on its correct use at monthly follow-up visits. Site staff also counseled participants on how to reinsert the ring should it come out accidentally between visits. Participants were encouraged to return to the clinic at any time if they had any difficulty in using the ring.

16. What was done to ensure the safety of participants in ASPIRE?
ASPIRE was designed based on rigorous international medical practice and ethical standards and conducted with numerous measures to protect the safety and well-being of participants. Potential volunteers were carefully screened by study staff to ensure that only women for whom it would be safe to participate were enrolled. Clinical teams at the trial sites performed thorough evaluations of participants at each study visit. A team at the MTN statistical and data management center (SDMC) assessed incoming reports on a daily basis, and an ASPIRE protocol safety review team (PSRT) provided regular monthly oversight. The PSRT includes physicians specializing in infectious diseases and HIV and in obstetrics and gynecology, whose sole responsibility is to ensure that everything possible is being done to monitor and protect the safety of participants.

Regular reviews were also conducted by an independent Data and Safety Monitoring Board (DSMB) that oversees clinical trials funded by NIAID to ensure that participants are not being adversely affected by the study or study products. The DSMB for ASPIRE conducted five reviews during the course of the study and never indicated any concerns about safety, quality of conduct or study integrity.

17. What happened if a participant became HIV-positive while in ASPIRE?
Despite the study's intensive efforts to reduce participants' risk of HIV, some women could become infected during the study due to sexual activity with an HIV-infected partner. Women in the trial who tested positive for HIV were taken off study product immediately and were counseled and referred by study staff to local HIV care and support services. Women were encouraged to remain in the ASPIRE study and continue with routine study visits but were also invited to participate in another MTN study called MTN-015. MTN-015 did not provide HIV treatment, but frequent laboratory tests indicating how the disease is progressing and how women are responding to treatment may have helped local treatment providers better manage their clinical care.

18. How could a woman become HIV-positive while taking part in an HIV prevention trial?
In sub-Saharan Africa, a woman's risk for acquiring HIV through sexual intercourse is greater than in any other part of the world. Participants in HIV prevention trials like ASPIRE are reminded of the fact that the product being tested has not been proven effective and that not all women in the study may be using an active product. To reduce the risk of HIV for women participating in its trials, MTN researchers provide trial participants free condoms, frequent HIV testing and HIV risk-reduction counseling, including on the correct and consistent use of condoms, and provide routine testing and treatment for STIs. Despite these intensive, ongoing efforts, a woman who participates in a trial like ASPIRE could acquire HIV if she has unprotected sex with a partner who is infected with the virus.

19. Was there concern that women who acquired HIV would develop drug resistance to dapivirine?
It's important to understand that drug resistance is possible only in someone infected with HIV, and ASPIRE's primary interest was in reducing HIV risk in all participants. However, if, despite the study's efforts, a woman

became infected, safeguards were in place to minimize the potential for drug resistance. For instance, women in ASPIRE were tested for HIV at every monthly visit. If a test indicated that a woman had acquired HIV, staff immediately stopped her use of study product, because its continued use could potentially increase the chance of virus becoming resistant to the drug. Women testing positive for HIV were monitored for resistance, even after stopping product, so that if identified, it could be managed appropriately by those treating the infection. Although dapivirine is not used in the treatment of HIV, ARV drugs in the same class as dapivirine (NNRTIs) are. At the same time, a potential advantage of dapivirine is that it remains potent even in the presence of common HIV strains with resistance to other ARVs. The ASPIRE trial will help to understand the nature and frequency of drug resistance among women who became infected while enrolled in the study.

20. Did ASPIRE provide antiretroviral therapy, or ART, to women who acquired HIV?
MTN receives funding to conduct clinical trials only, and is not permitted to provide HIV treatment. However, all MTN trial sites are required to have agreements with local service providers so that if a study participant acquires HIV she can be referred to the appropriate services and care in her community. In addition, site staff offered women the opportunity to participate in another MTN study, MTN-015. Frequent laboratory tests in MTN-015 indicating how the disease is progressing and women are responding to treatment may help local treatment providers better manage their clinical care.

21. What is adherence and why is it so important?
In the context of HIV prevention research, adherence refers to a person's willingness or ability to correctly and consistently follow a prescribed regimen. When participants use the study product as directed in an HIV prevention trial, researchers can determine with greater certainty whether the product prevents HIV. Moreover, no matter how effective a given product or approach may be, there's no benefit if it's not used. Women who need safe and effective HIV prevention methods must also be willing and able to use them. As such, a finding of low adherence in a clinical trial could also be an indicator of the kinds of challenges that women may face in the "real world."

22. What was done in ASPIRE to help women in using the ring consistently?
First, it's important to point out that the dapivirine ring is a long-acting product – to be used by women for four weeks at time – which may be easier and more convenient for women to use consistently. Still, site staff went to great effort to help trial participants and local communities understand the importance of correct and consistent product use and the impact that non-adherence can have on the findings of a research study. Indeed, many of the trial sites that conducted ASPIRE also had conducted the VOICE study, the results of which have had a significant impact on the design and conduct of other HIV prevention trials. Although in VOICE adherence was estimated to be about 90 percent based on what participants themselves had reported and on counts of unused applicators and leftover pills, blood tests conducted at the end of the trial revealed that only about 25 percent of the women had actually used product regularly. So, in ASPIRE, site staff devised social events and group meetings to help participants be more open about any difficulties with using the ring, other events either included or were exclusively for male partners. In addition, as the study was ongoing, blood samples and used rings were tested on a routine basis and the data pooled according to trial sites or the study overall so that challenges with use could be addressed as they occurred, but without compromising the blinded, placebo-controlled nature of the study.

23. How was adherence measured in ASPIRE?
Information about adherence to product use was collected using different measures in ASPIRE, including through face-to-face interviews and the use of Audio-Computer Assisted Self Interviewing (ACASI), which allows participants to answer questions about condom use, sexual behavior and product use. Tests that detect the presence of drug in blood and vaginal fluid samples taken from participants during the study will help determine how well participants followed the study regimens but also whether regular ring use is associated with HIV protection. Researchers will also examine tests conducted on used rings to determine whether drug has been released, an indication of ring use.

To better understand women's adherence to ring use as well as women's experience, indepth interviews and focus group discussions were conducted among 214 ASPIRE participants at select trial sites. Among the topics explored were women's experiences in using the ring, including any challenges they may have had in using the ring, such as

during sex or with menses, and their partners' knowledge of study participation as well as their views of the ring. Participants were also asked about their preferences for different kinds of products for HIV prevention, their willingness to use a ring in the future and issues related to "real-world" use.

24. What happened to women who became pregnant?
Researchers don't yet know how dapivirine might affect a woman's pregnancy or the development of her fetus, so trial participants must not have planned to become pregnant during the study and were required to use effective contraception and have monthly pregnancy tests. If a participant became pregnant during the study, she stopped use of the ring, but could remain in the study and continue with all trial site visits. She was also referred by study staff to available sources of medical care and other services that she or her baby may have needed. Depending on the timing of pregnancy relative to the study's progress, some women were able to resume using the ring, provided they were no longer breastfeeding. Women who became pregnant were also invited to participate in an observational study, MTN 016, or EMBRACE (Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure) that seeks to learn if whether the use of different ARV-based products being tested as HIV prevention can affect a woman's pregnancy outcome or her baby's general growth and development.

25. What were the medical benefits for women participating in the study?
Study participants received free laboratory tests and physical and pelvic exams, HIV prevention counseling and free condoms. STI risk-reduction counseling, testing and treatment were also provided at no charge to women, and HIV testing and STI treatment was offered to their partners as well. In addition, ASPIRE 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.

26. Why was ASPIRE only conducted in Africa?
The MTN has clinical trial sites in many parts of the world, but not all of these sites are in places where the rates of new HIV infections for women are as high as they are in Africa. In places where the risk for HIV infection is high, researchers can determine more quickly and with greater certainty whether a certain product is working. More importantly, women in sub-Saharan Africa represent the largest and fastest growing at-risk population for HIV, and they have the most to gain if this trial or any other trial identifies a safe and effective method for preventing HIV.

27. How did ASPIRE involve the community?
True community participation in HIV prevention research requires a level of ownership throughout the research process. Understanding the purpose, methods and limitations of clinical research is also vital for meaningful community input into study design and implementation. As such, all MTN trial sites have active community engagement programs with local non-governmental organizations, activist groups, journalists, local physicians, health department officials and other stakeholders; and during the development of an MTN protocol and throughout implementation, trial site Community Advisory Boards (CABs) play an especially important role. At a broader level, MTN's Community Working Group (CWG), comprised of a community educator and CAB member from each clinical research site, has and will continue to be actively involved in the development of community education strategies and in providing input about different study procedures. As the trial was being designed, leading African advocates and civil society representatives were also consulted. The MTN values their continued engagement, especially in the context of a changing HIV prevention trials landscape.

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More information and materials about ASPIRE are available at http://www.mtnstopshiv.org/news/studies/mtn020

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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