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QUESTIONS AND ANSWERS

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

I. ASPIRE and The Ring Study: The Basics

1. What was the aim of ASPIRE and The Ring Study?

As Phase III clinical trials, ASPIRE and The Ring Study were designed to determine whether a vaginal ring containing an antiretroviral (ARV) drug called dapivirine is safe and effective in protecting women against HIV when used for a month at a time. These trials also sought to determine whether women find the vaginal ring practical and easy to use. As sister studies, ASPIRE and The Ring Study were designed as the centerpiece of a broader licensure program to provide the strength of evidence to support potential licensure of the dapivirine vaginal ring for preventing HIV in women. Because at least two Phase III efficacy trials are usually 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.

2. What is a vaginal ring?

Vaginal rings are flexible products that fit high inside the vagina and allow for the slow, continuous delivery of a drug or multiple drugs over a period of weeks or months. In the U.S. and Europe, vaginal ring products are licensed for both contraception delivery and hormone replacement. Women can insert and remove the ring themselves.

3. What exactly is the dapivirine vaginal ring?

The dapivirine ring is designed to offer potentially long-acting protection against HIV. Each ring contains 25mg of the ARV dapivirine. When placed inside the vagina, the ring slowly releases the drug over the course of four weeks. The ring is made of flexible silicone and measures 56mm (about 2 ¼ inches) in diameter and 7.7mm thick (3/8 inch).


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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, one of the Janssen Pharmaceutical Companies, for use in the treatment of HIV. In 2004, Janssen granted a royalty-free license to the International Partnership for Microbicides (IPM), a non-profit product development partnership based in the U.S. and South Africa, to develop dapivirine as a microbicide for women in developing countries. That license has since expanded to an exclusive worldwide rights agreement. Studies have shown that the ring can deliver dapivirine to vaginal tissue for a month or longer with low absorption elsewhere in the body. Studies to date have also shown the ring to be safe and well-tolerated by women.

4. Who conducted and funded ASPIRE?

ASPIRE – A Study to Prevent Infection with a Ring for Extended Use, 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). Jared Baeten, M.D., Ph.D., of the University of Washington, is protocol chair; and Thesla Palanee-Phillips, Ph.D., of the Wits Reproductive Health and HIV Institute, South Africa, is protocol co-chair. As the dapivirine ring's developer and regulatory sponsor, IPM provided both the placebo rings and the rings containing dapivirine for use in ASPIRE.

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5. When and where was ASPIRE conducted? Who participated?
ASPIRE was conducted at 15 NIAID-funded clinical research sites in Malawi, Uganda, South Africa and Zimbabwe between August 2012 and June 2015, and enrolled 2,629 sexually active HIV-negative women ages 18-45 (272 in Malawi; 1,426 in South Africa; 253 in Uganda; and 678 in Zimbabwe). The population of women enrolled in ASPIRE is representative of women at risk in their communities:

6. Who conducted and funded The Ring Study?
The Ring Study, also known as IPM 027, is a study being conducted by IPM, a nonprofit product development partnership with offices in the United States and South Africa. The Ring Study, as part of IPM's overall dapivirine ring development program, has been supported by governments, multilateral organizations and foundations including, the Ministry of Foreign Affairs of Denmark, Flanders Department of Foreign Affairs, Irish Aid, the Ministry of Foreign Affairs of the Netherlands, the Norwegian Agency for Development Cooperation (Norad), the United Kingdom Department for International Development (DFID), the American people through the United States Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief (PEPFAR), and the Bill & Melinda Gates Foundation.

7. When and where is The Ring Study being conducted? Who participated?
The Ring Study began in April 2012 and enrolled 1,959 HIV-negative women at seven research centers – six in South Africa and one in Uganda. The study completed enrollment in November 2014, and is scheduled to conclude in December 2016.

8. What are the results of ASPIRE and The Ring Study?
ASPIRE and The Ring Study each found that the monthly dapivirine vaginal ring can safely help prevent HIV infection in women. In ASPIRE, the dapivirine ring reduced the risk of HIV infection by 27 percent overall, and in The Ring Study, infections were reduced by 31 percent. ASPIRE showed a greater level of protection for women over 21 – 56 percent – which was supported by a trend in The Ring Study, exhibiting more protection for women in that age group at 37 percent. Across both studies, the ring showed little to no protection in women ages 18-21. In ASPIRE, women over 21 were more likely to use the monthly ring with consistency, which may help explain why HIV protection was higher for them; The Ring Study showed a similar trend toward higher levels of protection with more consistent ring use. Taken together, these data suggest that the ring needs to be used consistently to achieve protection.

There were no safety concerns associated with the dapivirine ring in either study, and among women who acquired HIV, there were no differences in the number of cases or type of drug resistance between the dapivirine and placebo groups in each study. While much of the acceptability data is still being analyzed, anecdotal information suggests women found the ring convenient; many women reported they forgot they were using it .

9. How is it that The Ring Study has results before the scheduled end of the study?
Although still ongoing, The Ring Study is reporting results early, following a recommendation of by its independent data and safety monitoring board that the study proceed to final analysis. In February March 2016, after receiving feedback guidance from regulatory authorities in South Africa based on the safety and efficacy findings from both studies, The Ring Study began will begin closing its placebo arm in that country and offering women still enrolled in the study the active dapivirine ring for the remainder of their participation. IPM is seeking similar approval in Uganda.

10. What is the significance of these results – why are they important?
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. Despite tremendous advances in preventing and treating HIV, women still face disproportionate risk, and a number of current prevention options are not practical or usable by many women.

Daily use of an ARV tablet (an approach called pre-exposure prophylaxis, or PrEP) has been proven to be very effective in multiple populations at risk of HIV. South Africa and Kenya recently joined the United States in approving Truvada as PrEP, and in September 2015, the World Health Organization recommended that PrEP be offered to all persons at substantial HIV risk. But products must be used to be effective, and many women in the VOICE and FEM-PrEP studies – as well as in FACTS 001 –were not able to use the products (tablets or vaginal gel) sufficiently to provide protection against HIV.

No one method will suit everyone, nor suit everyone at all times within their lives. PrEP may be right for some women, but not all. As with contraception, the more HIV prevention options available to women, the more likely one will be used. The results of ASPIRE and The Ring Study suggest the dapivirine vaginal ring has the potential to help make a difference in reducing the burden of HIV in women. At the same time, both studies have also demonstrated that more must be done to address the HIV prevention needs of younger women, who remain one of the highest at-risk groups.

11. What happens next for The Ring Study?

IPM has received approval from the Medicines Control Council in South Africa to close the placebo arm of The Ring Study in that country and provide women still enrolled in the study the active dapivirine ring to use for the remainder of their participation. Approval to do the same is being sought in Uganda. IPM is also awaiting regulatory approval to conduct an open-label extension (OLE) study called DREAM that would provide women who already have completed participation in The Ring Study with access to the dapivirine ring. DREAM is designed to help answer critical questions about the product and its use once women are aware of its safety and efficacy.. In parallel, IPM, as the ring's developer and regulatory sponsor, plans to seek regulatory approval for the dapivirine ring's licensure, based on the results of The Ring Study and ASPIRE as well as several smaller safety studies conducted in or still taking place in the United States (including through the MTN) and Europe.

12. What happens next for ASPIRE?

For its part, the National Institute of Allergy and Infectious Diseases (NIAID), the primary NIH institute that funds the MTN, has indicated it will convene a panel of experts in March to provide advice on the future of NIH-funded dapivirine ring research. Depending on the outcome of these deliberations, two MTN studies could move forward. MTN-025, or HOPE, would provide former ASPIRE participants access to the dapivirine ring, and as a research study, gather additional data on the safety of and adherence to the ring. The second study, MTN-034, would seek to better understand the HIV prevention needs and desires of adolescent girls and young women (ages 16-21) and specifically, safety of and adherence to both the dapivirine ring and oral Truvada.

II. ASPIRE Results in Detail

13. When and where were ASPIRE results reported?

Results of ASPIRE, as well as The Ring Study, were announced at the Conference on Retroviruses and Opportunistic Infections (CROI)) in Boston on February 22, 2016. ASPIRE results were also published online in the *New England Journal of Medicine* the same day.

14. How was ASPIRE designed?

As a Phase III trial, women who enrolled in ASPIRE were randomized into one of two study groups, with one group of women assigned to use the dapivirine ring throughout the study, and the second group assigned to use a placebo ring that looked the same but contained no active drug. Participants received a new ring at every monthly clinic visit while in the study, which was at least one year and averaged of 18 months; those who enrolled earlier in the study used their assigned ring for up to 34 months. Because the study was "double blinded," neither participants nor researchers knew who was in which group during the study. All participants received ongoing HIV risk reduction counseling, condoms and diagnosis and treatment of sexually transmitted infections (STIs).

15. How was effectiveness determined?

To determine whether the ring was effective in preventing HIV, researchers compared the number of HIV infections that occurred in each group. Overall, 168 women in the study acquired HIV – 97 in the placebo group and 71 in the dapivirine ring group, representing a 27 percent relative reduction in HIV infection rates. An additional analysis, which was planned early into the study, excluded data from two of the trial's 15 sites that had less than ideal retention and adherence. In that second analysis, there were 139 HIV infections – 85 in the placebo ring group and 54 in the dapivirine ring group, resulting in a 37 percent reduction in HIV infections. Results of both analyses were statistically significant. Additional analyses found the reduction in HIV risk exceeded 50 percent in women older than age 21.

16. How was age related to HIV protection?

In a pre-planned analysis, women in the dapivirine group who were 25 and older were found to be 61 percent less likely to acquire HIV than women of the same age in the placebo group. Intrigued with this result, the researchers decided to conduct additional analyses. These drew a more precise line of demarcation, with lack of protection being confined to women between the age of 18 and 21, and women older than 22 seeing their risk of HIV cut by more than half (56 percent). The risk of HIV was reduced significantly more among the study's older participants, who also used the ring most consistently based on objective markers of adherence.

17. Why wasn't the ring effective in women under age 21?

While adherence was lower among women 18-21, poor adherence may not be the only reason that the ring was not effective in this age group. Further research is needed to understand if there are biological or physiological factors that may affect how dapivirine is taken up in vaginal tissue, or whether the trial design itself intimidates young women. Not knowing whether they are using an active product or a placebo, or whether or not the investigational product itself is safe and effective, may have been an influence. Interestingly, in open-label studies of Truvada as PrEP, both adherence and effectiveness were higher than in the original Phase III trials. Similar studies would be needed to determine whether the same would be true of women, including young women, and the dapivirine ring.

18. What role did adherence play in HIV protection?

ASPIRE found that HIV protection was greater in groups with evidence of better ring use. Incidence of HIV was cut by more than half – by 56% -- among women 21 and older, who as a group, appeared also to use the ring most consistently.

19. 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 in used rings were also used to help determine women's use of the ring.

20. What are researchers doing to understand more about what women truly thought of being in ASPIRE and using the dapivirine ring?

As part of ASPIRE, in-depth interviews and focus group discussions were conducted among 214 ASPIRE participants at six of ASPIRE's 15 sites in each trial-site country, to better understand women's adherence to ring use, their experience in using the ring, 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. Results from this qualitative data are being compiled now. Meanwhile, a similar study, MTN-032, will be conducted after women who had participated in ASPIRE have learned the study's results, to gain greater insight into the particular factors that may have motivated women to use the ring or stood in the way.

21. What did ASPIRE find related to the safety of the dapivirine ring and drug resistance?

The study found no safety concerns associated with the dapivirine ring, and among women who acquired HIV during the study, there were no differences in the number of cases or type of drug resistance between the dapivirine and placebo groups.

22. How can you really know the ring prevented HIV if everyone used condoms?

As in all HIV prevention trials, researchers conducting ASPIRE provided participants free condoms and HIV risk-reduction counseling, among other measures, for reducing their risk of HIV. We know however, that many women may not always convince their partners to use condoms. Despite all that was provided to study participants, the reality is that some women will still acquire HIV, and this will be true across study groups. So, at the end of the study, comparing the number of women in the group using the active product who get infected with the number who get infected in the placebo group is still a reliable way to indicate whether or not the product helps protect against HIV.

23. Were there differences in outcome by country?

ASPIRE found no differences in HIV protection with the dapivirine ring by country.

III. Implications and Next Steps

24. Will IPM be seeking regulatory approval? If so, where and when will the ring be available for widespread use?

IPM plans to seek regulatory approval for the dapivirine ring's licensure, based on the results of The Ring Study and ASPIRE as well as several smaller safety studies taking place in the United States and Europe. IPM anticipates being able to submit a comprehensive dossier of evidence on the ring to regulators early 2017. The regulatory review process takes time, and there is no guarantee of the ring's approval.

25. Are results of other studies required before submitting for regulatory approval?

Yes, 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. In MTN-029/IPM 039, researchers are looking to understand whether dapivirine gets absorbed by breastmilk; women who are no longer breastfeeding but are still able to produce breast milk will be enrolled. Among IPM's completed or ongoing studies are those looking at condom functionality, possible drug interactions and effects of menses and tampon use.

26. Would an open-label extension trial delay the timeline for regulatory submission and potential approval?

No. IPM intends to seek regulatory approval for the dapivirine ring's licensure in parallel with either or both open-label trials, pending their approval.

27. What is being done to better understand and meet the needs of adolescent girls and young women– those under age 21?

The MTN has developed a protocol, MTN-034, that would evaluate both daily oral PrEP and the monthly dapivirine vaginal ring in adolescent girls and young women ages 16-21 at trial sites in Africa. Participants would have the opportunity to use each product, and there would be no placebo. If implemented, the study would help in understanding what young women want, how they respond to use of these products when they know they are getting active products and their preferences for either or both approaches. . In addition, this study would explore possible biological reasons that may help to explain the high risk of HIV in young women. MTN researchers are already conducting a study called MTN-023 evaluating the safety and drug absorption qualities of the dapivirine ring in 96 adolescent girls in the United States.

28. Are there plans to develop a higher-dose dapivirine ring?

The ring evaluated in ASPIRE and The Ring Study contained 25 mg of dapivirine. Based on the results of these two studies, IPM is taking steps to seek licensure of the 25 mg dapivirine ring. At the same time, IPM is currently developing a ring containing 200 mg of drug that could potentially support use for up to 90 days. As with any new product, its testing must be done in step-wise fashion, beginning with Phase I safety trials in small groups of women. The MTN, in partnership with IPM, plans to conduct two such studies, including one that will evaluate a ring containing both dapivirine and the hormonal contraceptive levonorgestrel, a product that could provide protection against both HIV and unwanted pregnancy.

29. If approved, how much will the ring cost?

IPM is working with donors, governments and commercial manufacturers and other partners to develop the lowest and most cost-effective process possible, should the ring be licensed for use. Costs could vary from country to country and depend on factors such as the scale of manufacturing, delivery and packaging, and volume. Currently, the expected initial cost of the dapivirine ring is US$5 per ring compares favorably to PrEP. Further research and innovative financing mechanisms could further reduce the cost to women.

30. What studies of the dapivirine ring have been conducted by the MTN or are ongoing?
Other studies of the dapivirine ring conducted by the MTN include MTN-024/IPM 031, which evaluated its safety and drug absorption in post-menopausal women, with results also being reported at CROI. A similar study in adolescent girls, MTN-023/IPM 030, is being conducted in collaboration with the Adolescent Trials Network for HIV/AIDS Interventions. In MTN-029/IPM 039, researchers are looking to understand whether dapivirine gets absorbed by breastmilk; women who are no longer breastfeeding but are still able to produce breast milk will be enrolled. Two other early phase studies will evaluate different dosage formulations of the dapivirine ring (MTN-036/IPM 047) and a ring containing both dapivirine and the hormonal contraceptive levonorgestrel (MTN-030/IPM 041), a product that could provide protection against both HIV and unwanted pregnancy.

IV. At the Trial Site

31. What approvals were needed to conduct these studies?
ASPIRE underwent extensive and rigorous review by NIAID and the U.S. Food and Drug Administration. 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.

32. 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 prior to enrollment, and was revisited throughout the study. Information was provided in simple terms and translated into local languages.

33. 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 have 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.

34. What was done to ensure the safety of participants in ASPIRE and The Ring Study?
ASPIRE was designed based on rigorous international and local 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 at each of these reviews did not raise any concerns about safety, quality of conduct or study integrity.

35. What happened if a participant became HIV-positive?
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, to assess what effect, if any, use of the ring impacts disease progress or treatment response.

36. How could a woman become HIV-positive while taking part in an HIV prevention trial?
Participants in HIV prevention trials are already at high risk of acquiring HIV, and to help reduce their risk, researchers provide them with free condoms, frequent HIV testing and HIV risk-reduction counseling and 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.

37. What was done to help women in using the ring, and in using it consistently?
Many of the trial sites that conducted ASPIRE also had conducted the VOICE study, the results of which suggested important changes in the design and conduct of trials so that more accurate and meaningful information about adherence is collected, including during the trial. In ASPIRE, site staff conducted social events and group meetings to help participants feel comfortable in talking about any difficulties with using the ring; other events were conducted that either included or were exclusively for male partners, as they can often be key supporters (or challenges) to study participation. In addition, as the study was ongoing, blood samples and used rings were tested for dapivirine levels on a routine basis. Data within each site was pooled (not reported at the participant level) so that challenges with use at a site-level (or for the study overall) could be addressed as they occurred, but without compromising the blinded, placebo-controlled nature of the study.

38. Why were participants required to use contraception? What methods were they offered?
There is no information about how dapivirine might affect a woman's pregnancy or the development of her fetus, so to be eligible for the trial participants must not have had plans to become pregnant during the study, were required to be on effective contraception, and agree to have monthly pregnancy tests. Participants were offered a range of different options, including intrauterine device devices (IUDs), implants, injectable contraceptives and oral contraceptives.

39. What happened to women who became pregnant?
Participants who became pregnant during the study, stopped use of the ring, but could remain in the study and continue with all trial site visits. They were 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, 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.

40. What were the medical benefits for women participating in these studies?
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.

41. Why was ASPIRE only conducted in Africa?
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. 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.

42. How were trial site communities involved?

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 Advisory Boards (CABs) and community engagement programs for building and sustaining partnerships with local non-governmental organizations, civil society, news media, local physicians, health department officials and other stakeholders, and seeking their involvement during the development of a study protocol, study implementation through to results dissemination.

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More information and materials about ASPIRE are available at http://www.mtnstopshiv.org/news/studies/mtn020
More information about The Ring Study and the dapivirine ring can be found at at 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.

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