Questions about being exited from the study

Why do I have to exit the HOPE study now when other women are still continuing study visits?
You are exiting the study now because you have completed approximately a year of follow-up. The HOPE study was designed so that all women who enroll participate for the same amount of time – about one year. This means that participants will exit the study at different times depending on the date they enrolled into HOPE. Women who are continuing with study visits now have not yet reached their one year of follow-up time like you have. When they reach this milestone, they will be exited as well. (Note that some women who enrolled very late may participate in HOPE for less than one year. These women were told about this shortened follow-up time before they agreed to enroll in the study.)

You have contributed a lot of information during this one year and we want to thank you for all your efforts.

Why was HOPE designed to be only one year of follow-up?
The HOPE study was designed to provide former ASPIRE participants the opportunity to use the dapivirine ring in the context of a study that would build on the results of ASPIRE. In HOPE, we are learning more about the ring's safety, how women use the ring knowing that it can help reduce their risk of acquiring HIV, and the relationship between adherence and HIV protection. We also want to understand the reasons why some participants who took part in ASPIRE choose not to enroll in HOPE, and why some women who enroll in HOPE do not want to use the ring.

The researchers who designed HOPE determined that a follow-up period of one year for each participant would provide enough data to answer the study's questions within a timeframe that could help inform ongoing drug regulatory submissions. If the ring is approved, HOPE will also help provide information for rollout into communities. HOPE is similar to other HIV prevention open label extension studies that have been conducted to date, which lasted between one and two years. [TDF2 – 1 year; Partners PrEP Study Extension- 1 year; iPrEx – 18 months; CAPRISA 008 – 2 years]. It is important to note that HOPE is happening at the same time as ongoing regulatory submissions, and does not lengthen the regulatory approval timeline.

If the ring is effective, why may some participants seroconvert in HOPE?

There are several reasons why some participants may seroconvert even if they are participating in HOPE:

- We know that the ring reduced women's risk of acquiring HIV in previous clinical trials, and that protection appeared to be highest when the ring is used all the time, but the ring is not 100% effective. This is why women are counseled on all of the available HIV prevention methods—for example, using condoms, reducing the number of sexual partners, getting testing and treatment for STIs—and encouraged to use as many of these risk reduction strategies as possible to lower their chance of HIV infection.
- We also know that not all participants who join HOPE choose to accept the ring, and not all women who take a ring are able to use it with high adherence. Trained counselors work with each participant to help her choose the HIV prevention plan that she feels will work best for her, and work with her to reduce any barriers to succeeding with this plan. Even so, not all women in HOPE are able to adhere to their HIV prevention plans with perfect adherence, whether it includes the ring or not.
- Finally, there may be some women who were already infected with HIV at the time they enrolled in HOPE, even though testing at enrollment was negative. For these women, they would only find out that they were HIV positive after participating in HOPE for 1-3 months. This is because when a person is first infected with HIV, it takes time for their body to develop a response to the virus, which causes a delay in the ability of an HIV test to detect infection. This is called the 'window period' and this is why it is important to get frequent HIV testing, even if you have recently had a negative test.

Why can't women have access to the ring until it's approved and available?
The ring has not yet been approved by regulatory authorities, so we can only provide the ring to former ASPIRE participants in the context of HOPE, which was designed as a one-year study. After exiting HOPE, participants would only have access to the ring if and when it is approved and made publicly available.

Aren't you concerned that women will become infected after they exit HOPE? What are you doing to ensure women don't become infected during this time? Once I am no longer in the study, how will I be protected from HIV?
Yes, we are concerned. We acknowledge that for our participants, the reality is that they live at high risk of acquiring HIV and their options for protection are limited. That is exactly why we are doing this work—to expand the prevention options available to women in our communities. Before exiting the study, participants will receive counseling on different HIV prevention options, including how to access certain services after they leave the study. Options may include: using condoms correctly and consistently, using oral PrEP (if accessible in your country either through private or public referrals), reducing the number of sexual partners, engaging in lower-risk sexual behaviors, having frequent HIV and STI testing (and receiving treatment for STIs, if infected), and encouraging their partners to get testing and treatment for HIV and STIs. Additionally, women can help their partner(s) lower their risk by encouraging them to be circumcised. Although all options may not be possible for all people, the more of these things a person can do, the lower their chance of getting infected with HIV.

What about Oral PrEP? Is this an option that I can access now to protect myself?
Oral PrEP for HIV prevention is a strategy that involves daily use of antiretroviral medication by people who are HIV negative. PrEP is very effective in reducing the risk of acquiring HIV infection when used consistently. PrEP is increasingly becoming available and many countries are actively developing national policies and plans for access – *refer to site SOPs for more specifics*.

Are there other HIV prevention research studies that I can join?
[For sites with other ongoing studies:] There may be other HIV prevention research ongoing at this site or at research centers nearby. If you are interested, we can provide you with information about this research *[sites to include details on studies that are recruiting or upcoming in the area]*. Many studies will require that you wait a certain amount of time between studies. If this time has passed, and you meet other eligibility criteria, you may be able to enroll in another research study.

[For sites without other ongoing research]: At this time, there are no other HIV prevention studies ongoing at this site or at research centers nearby. If you are interested in participating in potential future studies, please be sure to let staff know so that your contact information can be kept up to date. Should there be a study that you may be eligible for in the future, we will reach out to you and provide you with information about this research.

When will results from HOPE be available? How will I be informed of these results?
All HOPE study visits will be completed by the end of September 2018, and results would be available some time in 2019.

As soon as results are available, site teams will reach out to HOPE participants to share this information. Sites will also conduct meetings and events to share results with participants and the community *[sites to outline any other dissemination activities*]. Please be sure to keep your contact information up-to-date at the research site so that we are able to share results with you in a timely fashion.

How can you tell me that I have made such an important contribution and not give me anything back?

We realize that it may be challenging to exit the study before you know when and how you will have access to the ring in the future. Please know that we are extremely grateful for the investment of time and energy that

you have given as a participant in both ASPIRE and HOPE. We greatly appreciate the commitment you and other participants have shown to these studies and, most importantly, in your dedication to doing everything you can to prevent HIV, not only for yourself, but for others in the community and around the world. We thank you for the trust you have given to the HOPE team, and your commitment to improving women's access to a greater variety of effective and safe HIV prevention options.

This process is complicated and takes time, but if the dapivirine ring receives regulatory approval and becomes available publicly, your investment in both ASPIRE and HOPE will have been a big reason why. We hope that you can feel proud of your participation and contribution. Even though we do not have the resources to continue making the ring accessible to you now, we hope the applications for regulatory approval will be successful and we can celebrate together the ring being an HIV option available to women.

Where will I get contraception?
Before you exit from HOPE, study staff will have a conversation with you about what contraceptive method you prefer, and how you can access this method after you exit the study. If you prefer to use a short-term method like the pill or injections, the site will make sure to refer you to a clinic or organization where you can keep accessing the method of your choice. If you are using a longer-term method, like the IUCD or implants, and wish to continue using this method after the study, site staff can give you a list of organizations where you may be able to have the contraceptive device removed or replaced the method you are using expires and when that time arrives for it to be replaced.

If you want to change or stop your current method of contraception before exiting the study, the study team will work with you to make this switch and make sure you know where to go for your future family planning needs in the local community setting.

Where will I get health care?
We understand that accessing good health care services can sometimes be difficult, whether it is for treatment of a minor injury or for testing and treatment of STIs. If you have any ongoing or chronic medical conditions, we will provide you with a referral to a clinic or hospital so that you can continue to receive care after you exit HOPE. If you have any medical needs that are typically addressed here at this clinic, the study team will also work with you to make sure these are resolved or managed before you exit HOPE.

If you develop a new injury or condition, or if you would like HIV or STI testing or treatment after you exit HOPE, and are not sure where to go, you can still call the research site and we may be able to help you find where to go for care. The study team wants to make sure you continue to get the care you need to stay healthy!

Questions about DREAM

What is DREAM?
DREAM (Dapivirine Ring Extended Access and Monitoring) is the open-label extension study for former participants in The Ring Study being conducted by IPM. As with HOPE, the DREAM study aims to collect extended safety information, explore when, why and how women use the ring, and help to understand how adherence may affect the product's efficacy, and ways to support ring use.

Where is DREAM being conducted?
DREAM is being conducted at former Ring Study sites – one site in Masaka, Uganda, and five sites in South Africa. These are Desmond Tutu HIV Foundation in Masiphumelele; Madibeng Centre for Research in Brits; Maternal, Adolescent and Child Health (MatCH) in KwaZulu-Natal; Ndlovu Care Group in Elandsdoorn, Limpopo; and Qhakaza Mbokodo (QM) research center in KwaZulu-Natal.

Is it true that DREAM will continue until a regulatory decision is made, and if the ring is approved, until it is publicly available?
IPM hoped to secure additional funds to continue DREAM until regulatory decisions were made in South Africa and Uganda (where The Ring Study took place and DREAM is currently ongoing). Unfortunately, the pace of donor funding is not at the level needed to support DREAM for longer than one year. During the consent process, participants were told that DREAM was designed so that all women participating in the study would use the ring for about a year – and that this period could be shorter or longer.

Questions about next steps/other studies of the ring

Are other studies of the ring being planned?
Yes.

REACH (Reversing the Epidemic in Africa with Choices in HIV prevention, or MTN-034) will evaluate how adolescent girls and young women age 16-21 use the monthly dapivirine vaginal ring and Truvada® as daily PrEP, and their preferences for either or both approaches. It will enroll approximately 300 girls and young women at five trial sites in Kenya, South Africa, Uganda and Zimbabwe. The study, which will start in 2018, will also collect much needed information on the safety of these HIV prevention methods in young women. This is especially important for the dapivirine ring. While IPM plans to seek regulatory approval for use of the dapivirine ring by women ages 18-45, data specifically on the ring's safety and use among women younger than 18 would be required if the ring will be made available to this population. The MTN has already completed a safety study of the ring (MTN-023 /IPM 030) among adolescent girls in the United States, which showed that the ring was well-tolerated and acceptable for younger women. The REACH study will contribute important data about the ring's use by African girls.

MTN researchers are also planning studies to be conducted here in Africa to determine whether the ring is safe to use by women during pregnancy and breastfeeding, when the risk of acquiring HIV from an infected partner may be particularly high.

While a ring used for a month at a time may appeal to some women, others may prefer a product they replace every three months, or a ring that provides contraception in addition to protecting against HIV. Studies of these next generation rings are ongoing or planned in the U.S., including a study of a three-month ring (MTN-036/IPM 047) and studies of the dual-purpose ring (MTN-030/IPM 041, MTN-044).

What is a demonstration project? Will there be demonstration projects for the dapivirine ring?
Demonstration projects look at how new interventions are working in more real-world settings. If the ring is approved, there will likely be interest in conducting demonstration projects. At this time, we are not aware of nor can we confirm any specific plans. Should we receive this information, we will be sure to let you know.

Will I be able to participate in any of these studies? Or in demonstration projects?
Just like HOPE and ASPIRE, each new study or demonstration project will have its own eligibility criteria that specifies who is able to participate. Depending on these eligibility criteria and whether you meet them at the time the project is taking place, you may or may not be able to participate. If you are interested in participating in potential future studies or demonstration projects, please be sure to let staff know and keep your contact information up to date. Should there be a project that you may be eligible for in the future, we will reach out to you and provide you with information about this research.

Questions about regulatory process and timelines

Do you think the ring will be approved?
We are hopeful the ring will be approved. IPM, the developer of the ring, is in the process of submitting applications to regulatory authorities to seek the ring's approval. These applications include data from ASPIRE and The Ring Study and may include data from the HOPE and DREAM open-label studies, when available. We should all feel proud of the contributions we have made to bring us to this point. It is now up to the regulatory authorities to decide whether to approve the ring.

Who decides whether to approve the ring?
It's a complicated process. In June 2017, IPM submitted its first regulatory application to the European Medicines Agency (EMA) through a procedure called Article 58, which provides a scientific opinion on the safety, efficacy and quality of medicines that would be marketed exclusively outside of the European Union—specifically in low- and middle-income countries—for diseases of major public health interest. A positive opinion from the EMA under Article 58 would help facilitate the ring's World Health Organization (WHO) prequalification, which many African regulatory authorities consider during their own product reviews and approvals.

IPM plans to submit next to the South African Health Products Regulatory Authority and then to the US Food and Drug Administration, followed by applications to national regulatory authorities in African countries, including those where previous studies of the dapivirine ring were conducted.

Ultimately, a decision whether to approve the ring in [country] will be the responsibility of [drug authority].

How does information learned from HOPE contribute to potential dapivirine ring approval and public access?
IPM began submitting its applications to regulatory authorities in mid-2017 as HOPE and DREAM are ongoing. Data from these studies will also be provided upon their completion or if requested during the review process. Both studies will provide important information that will help guide implementation of the ring should it receive regulatory approval.

What can we do to support the process of approving the ring in our country?
***For Non-South African Sites*:** The decision whether to approve the ring in [country] will be the responsibility of [drug authority], assuming first that it is supported by WHO pre-qualification . By participating in HOPE and ASPIRE you have made a great contribution to the process. It will now be up to the regulatory authorities to decide to approve the ring or not.

***For South African Sites*:** The decision whether to approve the ring in South Africa will be the responsibility of the South African Health Products Regulatory Authority. By participating in HOPE and ASPIRE you have made a great contribution to the process. It will now be up to the regulatory authority to decide to approve the ring or not.

When could the ring be available to women? Would it be available to HOPE participants before the general public?
The earliest that some African regulatory authorities would make a decision is in 2019. However, approval would not mean the ring's immediate availability. Governments would still need to decide if, how, and when they want to implement its delivery, and timelines and processes may differ across countries. The ring would be made available to former HOPE participants at the same time as other women.

-more-

Why does it take so long?
The application that IPM will be submitting to regulatory authorities contains data from more than 250 laboratory and clinical studies, detailing nearly 15 years of research. The length of the submission is 260,000 pages, and must be adapted to the requirements of each regulatory agencies. Regulators must then review all of this information carefully. Because dapivirine is a new drug, the process may be more complex than for a drug like Truvada, which was already approved for the treatment of HIV when it was under review for use as prevention.

What is the anticipated cost of the ring? Who would pay for it?
As a nonprofit, IPM's goal is to ensure the ring's affordable access. If approved, the ring would likely be publicly funded and provided to women at low or no cost, similar to other HIV prevention services.

Because I participated in ASPIRE and HOPE, will the ring be available to me at a reduced cost?
If the ring is approved, it will be available to you and other women at low or no cost, similar to other HIV prevention services.

Where would women get the ring? Would it be sold through private markets, distributed at hospitals, or some sort of combination of private and public partners?
The ring's distribution would vary from country to country. Because the dapivirine ring contains an ARV drug and will require regular HIV testing, some countries may require a health worker to prescribe or dispense the product to women. IPM continues to work with regulatory agencies, HIV prevention experts, local partners, advocates and others to identify appropriate distribution channels, and to develop marketing and public education campaigns for potential product rollout.

If the ring is licensed for HIV prevention, will this promote and increase risky sexual behavior?
As HIV prevention methods, family planning options, and sexuality education programs have improved over time, some groups have argued that these interventions – which can reduce the potential negative consequences of sexual activity – have the unintended result of increasing risky sexual behavior. So, it is not surprising that a similar concern is being raised about the dapivirine ring. However, extensive research has shown that improved access to sexual health information and services, such as HIV prevention methods, do not have the overall result of promoting riskier sexual behavior including increased number of sexual partners, decreased faithfulness, or increased frequency of sex.

For example, changes in sexual risk behavior in populations accessing oral PrEP have been examined in several trials. These trials have sought to examine the idea that introducing an effective HIV prevention method may increase risky behavior and potentially mitigate any benefits of the prevention method. This idea is known as 'risk compensation'. Oral PrEP was not associated with increased sexual risk behavior or sexually transmitted infections in these studies in the Americas and Africa. In fact, a recent study with women in Africa showed no increase in sexual risk behavior related to oral PrEP use. While current research points to risk compensation not being a cause for concern when it comes to PrEP use, ongoing demonstration projects will provide more information to evaluate this topic.

Similar questions have been raised after introduction of other interventions involving sexual behavior. For example, does increased access to female contraceptives promote risky sexual behavior, or will sexual health education for young people lead to earlier sexual debut or a greater number of sexual partners? While risk compensation was raised as a potential concern in all these examples, several studies have observed no increase in risk behaviors after introduction of these interventions. More than 1,000 World Health Organization reports on sex education programs indicate that such programming does not increase sexual risk behavior. Similarly, studies of family planning programs have consistently found that contraceptive access does not increase sexual risk-taking behavior.

With all the information we have now, it is clear that these new HIV prevention technologies do not encourage risky behavior. In fact, they provide our communities with more options to reduce risk and protect people from HIV. Nevertheless, working with community members who have this concern may still prove challenging due to deeply held traditional or religious beliefs. Organizations such as PATH, IntraHealth International, and Avert have developed extensive resources that sites can use to support changing beliefs about sexuality, HIV, and access to services. Please find a few links to these resources, as well as some of the studies cited for this response, below:

- Risk Compensation in PrEP
- HPTN 067 – Daily PrEP in Cape Town
- PATH
- IntraHealth International
- Avert

Questions about HOPE interim results

What are the HOPE interim study results?
The HOPE interim results are a mid-study assessment of data collected in MTN-025. Overall, the results show that there has been high uptake of and adherence to the dapivirine vaginal ring in HOPE. New HIV infections are occurring at about half the rate researchers would expect to see had women not been given the opportunity to use the ring in HOPE. The research team reported HOPE interim results at the Conference on Retroviruses and Opportunistic Infections (CROI) in March 2018

What data was used to calculate the interim results?
To calculate these interim results, researchers conducting the HOPE study used data collected between August 2016 and October 2017. By this time, 1407 former ASPIRE participants at 14 sites in Malawi, South Africa, Uganda, and Zimbabwe had enrolled in HOPE. Note that the HOPE study is ongoing and the last participants will exit the study around September/October of 2018. Once all participants have exited the study, the researchers will look at all the data collected during HOPE and final study results will be made available to you, should you want them.

What are the details of the interim results?
HOPE interim results specifically show that 92% of women who enrolled in the main study cohort chose to use the vaginal ring as part of their HIV prevention plan. Over time, some women modified their HIV prevention plans but 81% of participants were still choosing to use the ring by month 9. Out of those women who did choose the ring, residual drug levels show that 89% of rings were used at least some of the time – only 77% of rings showed this level of use during ASPIRE. At the time of the interim review, the rate of new HIV infections was 1.9, considerably lower than what was seen in ASPIRE. HIV incidence, which represents the number of women who are newly infected for every 100 participants in a given year, was 3.3 in the group of ASPIRE participants assigned to use the dapivirine ring and 4.5 among those in the placebo group. Using statistical modeling based on the placebo group in ASPIRE, the researchers estimated the rate of new infections would have been 4.1 had women otherwise not been able to take part in HOPE and be offered the ring. The difference in incidence rates represents a 54 percent reduction in HIV risk.

Interim results of DREAM, which were also reported at CROI, are remarkably similar. While these findings are encouraging, they must also be considered in light of inherent limitations, such as the lack of a true placebo group in either study.

Do the results include all women in the study, even those who were not using the ring?
The interim results include information gathered from all women participating in the main study cohort – both acceptors and non-acceptors. The researchers did not yet have enough data to look at the impact of ring use/adherence on HIV protection, so that analysis will be done at the end of HOPE.

Are there any limitations to these results?
There are some limitations to the analysis of the interim results. First, there is no placebo (control) group to use for comparing HOPE participants – it would not have been ethical to deny any study participants access to the ring given its safety and efficacy results in Phase III trials. Second, HOPE participants also participated in ASPIRE and may have a lower risk of acquiring HIV than estimated. Finally, HOPE is ongoing until September 2018 and we will continue collecting information until then. We will not know the final results of the study until all participants have been exited and researchers have been able to analyze all the data.

How does the HIV infection rate compare to other open label trials, like for oral PrEP?
The HIV incidence in HOPE so far is 1.9, which is similar to what was seen in other open label studies. For example, in iPrEx OLE, an open label study of oral PrEP, HIV incidence was 2.0 across the entire study.

What if women had used oral PrEP instead of the ring?
It is difficult to estimate what HIV incidence that would have been if participants were using oral PrEP instead of the ring, but just like the ring, oral PrEP requires good adherence in order to work. A large analysis of PrEP data collected across multiple studies suggests that HIV protection with oral PrEP (given variability in efficacy and typical use) may be about 50% in women, which is very close to what we are seeing so far in HOPE.

What about the interim results from DREAM?
DREAM interim results are very similar to the interim results found in HOPE. More information about DREAM can be found at www.ipmglobal.org.

Do these interim results impact the regulatory approval process or timelines?
Interim safety and ring use data from HOPE and DREAM may be of interest to regulators, as will final results. We cannot speculate what effect, if any, this may have on the approval process or timelines.