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HOPE open-label study of vaginal ring for preventing HIV begins for former ASPIRE participants

HOPE to learn more about adherence and safety of monthly dapivirine ring, and better understand why the ring may work well for some women but not for others

DURBAN, July 18, 2016 – Women who took part in ASPIRE, a trial that found a vaginal ring containing an antiretroviral (ARV) drug called dapivirine was safe and helped protect against HIV, will soon be offered the opportunity to use the ring as part of a new study called HOPE. The first of HOPE's sites opened just today, at the Medical Research Council of South Africa's Verulam clinical research site in KwaZulu-Natal. Other South African sites, and sites in Malawi, Uganda and Zimbabwe, will open in the coming weeks or months as in-country approvals are received and other requirements are met.

HOPE (HIV Open-label Prevention Extension, or MTN-025) 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.

The study also seeks to understand why the ring may work well as an HIV prevention strategy for some women but not for others. The dapivirine ring is meant to be used for a month at a time, and women can insert and remove it themselves. But this may not be for everyone, acknowledge the researchers from the U.S. National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN) who conducted ASPIRE and will run the HOPE study. For this reason, former ASPIRE participants may enroll in HOPE even if they do not wish to use the ring.

ASPIRE (A Study to Prevent Infection with a Ring for Extended Use, or MTN-020) involved 2,629 women ages 18-45 from Malawi, Uganda, South Africa and Zimbabwe and was conducted between August 2012 and June 2015 in parallel with a second Phase III trial, The Ring Study, led by the International Partnership for Microbicides (IPM). IPM developed the dapivirine ring and is the ring's regulatory sponsor.

Primary results of both studies were reported earlier this year. Across both studies, HIV risk was reduced by about one-third, meaning that one in three women who might have acquired HIV did not. In ASPIRE, there were 27 percent fewer women who acquired HIV in the group assigned to use the dapivirine ring than in the group who used a placebo ring with no active drug. HIV risk was reduced by more than half among participants older than 21, who also appeared to use the ring most consistently.

New results from exploratory analyses of data from ASPIRE reported today at The International Conference on AIDS (AIDS 2016) in Durban suggest even higher levels of protection can be achieved with regular and consistent use. Among women who appeared to use the ring most regularly, HIV risk was cut by more than half across all analyses, and in some, by 75 percent or more.

"The timing of these results could not be more perfect. The goal of HOPE is to offer women a product shown to be safe and able to provide some protection against HIV. When we were conducting ASPIRE, we did not know whether the ring would be effective for HIV prevention. Knowing the results of ASPIRE, it will be a totally new conversation with women in HOPE," said Jared Baeten, M.D., Ph.D., of the University of Washington, who led the ASPIRE study with Thesla Palanee-Phillips, Ph.D., M.Sc., of the Wits Reproductive Health and HIV Institute, Johannesburg, South Africa. "That we, as a field, are in a place to be able to offer women a product specifically designed for them is truly a significant milestone in HIV prevention."

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Drs. Baeten and Palanee-Phillips will also be leading the HOPE study, together with Nyaradzo Mgodi, MBChB, MMed, from the University of Zimbabwe-University of California San Francisco in Harare.

In other open-label extension studies 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 in the original Phase III trials. Whether this will hold true for the dapivirine ring in HOPE remains to be seen.

Unlike a Phase III clinical trial, there is no placebo group in an open-label study. In HOPE, all women, if they choose, receive the monthly dapivirine ring. Other aspects of the study are designed to help move toward a more "real world" delivery model. For instance, visits will be monthly for the first three months, and then quarterly thereafter. And while staff will counsel participants on the importance of adherence, they will also want women to feel empowered to make their own choices and to be open about the reasons they may or may not want to or be able to use the ring.

"It requires a whole new shift in mindset," explained Dr. Palanee-Phillips. "In ASPIRE, we counseled participants on the importance of adherence so we could establish whether the ring was safe and effective. If women didn't use their assigned rings in ASPIRE, we would not have been able to answer these critical questions. In HOPE, with the information we now have, we want women to understand that the importance of adherence is not about the trial, but about their own, individual protection."

"We want nothing more than for women in sub-Saharan Africa, and of course the world over, to have a means to be protected. While we are excited about the ring, it may not be the right approach for some women. Maybe they would prefer oral PrEP, or perhaps other approaches we are investigating, like long-acting injectables. It's really about giving women choices," added Dr. Mgodi.

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. A similar open-label extension trial for former participants of The Ring Study, called DREAM, is expected to begin soon at sites in South Africa and Uganda.

Both the HOPE and the DREAM open-label studies will be taking place at the same time that IPM is compiling comprehensive data on dapivirine and the ring, including findings from ASPIRE and The Ring Study, and from several smaller supporting studies, into an extensive dossier it expects to submit to regulators in 2017. If granted, the first regulatory approvals could be received as soon as 2018, within the same timeframe that results of both HOPE and DREAM may be available.

Vaginal rings are flexible products that fit high up inside the vagina where they release a medication slowly over time. The monthly ring tested in ASPIRE and The Ring Study, and offered to women in the HOPE and DREAM studies, contains an ARV drug, dapivirine, as a way to provide women potentially longer-acting protection against HIV.

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. Despite advances in preventing HIV, women – young women, especially – still face disproportionate risk, and a number of current prevention options, including oral PrEP, may not be accessible to or practical for many women. Ideally, women should be able to have choices when it comes to protecting themselves against HIV because no one approach will be right for all women, nor be right at all times in their lives.

Toward this end, MTN is planning a study (MTN-034/IPM 045) that will evaluate how adolescent girls and young women use the monthly dapivirine vaginal ring and Truvada® as daily PrEP, and their preferences for either or both approaches. The study will also examine whether certain biological or physiological factors affect how the active drugs are taken up in the body. MTN-034/IPM 045 will help to better understand the factors

that may have contributed to the ring not being effective among those ages 18-21 in ASPIRE. 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.

Dapivirine, also known as TMC-120, belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTIs) that bind to and disable HIV's reverse transcriptase enzyme, a key protein needed for HIV replication. The dapivirine ring's development was made possible by a public-private partnership between IPM and Janssen Sciences Ireland UC, a Janssen pharmaceutical company of Johnson & Johnson, which granted IPM a royalty-free license in 2004 to develop dapivirine as a microbicide for women in developing countries. That license has since expanded to a worldwide rights agreement.

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See also, Used consistently, monthly vaginal ring may be highly effective against HIV in women, suggest new analyses from ASPIRE

A backgrounder, After ASPIRE: HOPE and other MTN Studies of the Dapivirine Ring, and additional information about ASPIRE can be found at www.mtnstopshiv.org/news/studies/mtn020.

More information about The Ring Study and the dapivirine ring can be found at www.ipmglobal.org and Dapivirine ring may offer significant HIV protection when used consistently – new data

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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