Used consistently, monthly vaginal ring may be highly effective against HIV in women

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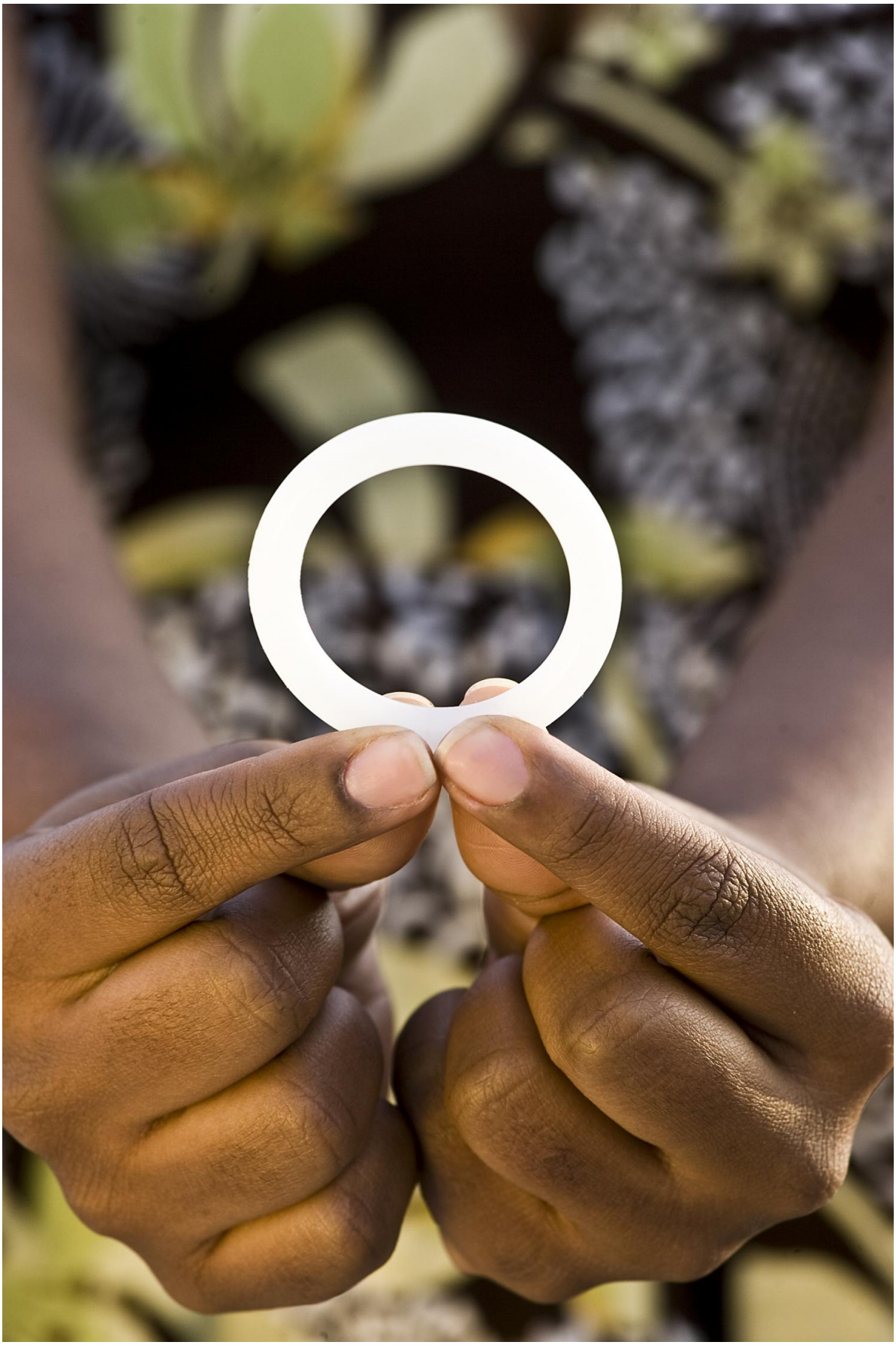

The monthly dapivirine ring, developed by the International Partnership of Microbicides (IPM). Credit: Andrew Loxley

When used consistently for a month at a time, a vaginal ring containing an antiretroviral (ARV) drug called dapivirine provides significant protection against HIV, suggest results of new data analyses from the ASPIRE study announced today at The International Conference on AIDS (AIDS 2016) in Durban, South Africa. 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.

ASPIRE - A Study to Prevent Infection with a Ring for Extended Use, or MTN-020, was a Phase III trial that involved 2,629 women ages 18-45 from Malawi, Uganda, South Africa and Zimbabwe. Its main results, which were reported earlier this year, found the dapivirine ring reduced the risk of HIV by 27 percent, meaning that 27 percent fewer women acquired HIV in the group assigned to use the dapivirine ring than in the group assigned to use a placebo ring containing no active drug.

The new results, which are based on additional exploratory analyses, suggest the dapivirine ring may be far more effective when used most or all the time, said researchers from the National Institutes of Health (NIH)-funded Microbicide Trials Network. They discussed their new findings today at an official AIDS 2016 press conference, and will present them during a scientific session at the meeting on Tuesday.

"Adherence to HIV prevention strategies is not always perfect, and we knew that not all women used the ring consistently, so we developed an analysis to explore the degree of HIV protection that was associated with

more consistent use," explained Elizabeth R. Brown, Sc.D., from the Fred Hutchinson Cancer Research Center and University of Washington in Seattle, who is the principal investigator of MTN's Statistical and Data Management Center (SDMC). "Across all analyses we saw high adherence was associated with significantly better HIV protection."

While these new results are encouraging, Dr. Brown and her colleagues are mindful that there are inherent limitations in these kinds of exploratory analyses, and that further study will be needed to validate the results.

Indeed, as the follow-on study to ASPIRE, HOPE (HIV Open-label Prevention Extension), or MTN-025, will be able to look more closely at the relationship between ring use and HIV protection. 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.

In HOPE, former ASPIRE participants will have the opportunity to use the dapivirine ring (there will be no placebo) in the context of knowing that it is safe and can help prevent HIV. HOPE will gather additional information on the ring's safety and how women use the ring. Acknowledging that the ring may not be for everyone, HOPE also looks to better understand why it may work well as an HIV prevention strategy for some women but not for others. As such, former participants may enroll in HOPE even if they do not wish to use the ring.

"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. 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 was protocol chair of the ASPIRE study and also leading HOPE.

Vaginal rings are flexible products that fit high up inside the vagina where they release a medication slowly over time. The ring tested in ASPIRE, and offered to women in HOPE, contains 25 mg of the ARV dapivirine, about 4 mg of which gets released over 28 days. The ring is meant to be used for a month at a time, and women can insert and remove it themselves. The dapivirine ring was developed by the nonprofit International Partnership for Microbicides (IPM), which is also the ring's regulatory sponsor.

Adherence was measured in ASPIRE by testing for the presence of drug in blood samples from women's quarterly visits, and beginning one year into the study, also by testing the amount of residual drug remaining in used rings that women returned to the clinic at monthly visits. The analysis presented at AIDS 2016 included 2,359 women and data from more than 12,000 returned rings.

The first analysis used two specific amounts of residual drug, 23.5 mg and 22 mg, to define adherence; a participant with a ring with any amount of drug below the cutoff was considered adherent. By this definition, adherence was associated with a reduction in HIV risk of 56 and 65 percent, respectively, compared to placebo, with both findings being statistically significant.

However, a single cutoff of drug cannot distinguish between women who may have used the ring just some of the time and those who used it all of the time. Moreover, without considering the length of time a participant had a ring, it was not possible to distinguish adherence based on remaining drug levels alone. While the regular visit schedule was every four weeks, women who were unable to make a particular visit could come earlier or later. This would mean, for example, that someone who might have exchanged her ring after three weeks of consistent use could be categorized similarly to someone who had the ring for six weeks with only partial use.

Dr. Brown, who led the investigation, developed a so-called time-varying model that could take into consideration how the drug gets released over the 28 days a ring is intended to be used, and the variability in duration that women may have had a ring. It also considered that women who tested positive for HIV at their monthly visit likely became infected in the prior two to 12 weeks; it would be important to "flag" rings they may have returned to the clinic during this period.

Using this model, researchers identified four different levels of adherence, from non-use to near perfect ring use, with a level of HIV protection for those who used the ring most consistently, ranging from 75 percent in one analysis to 92 percent in another, each with statistical significance.

In HOPE, researchers will be able to see if former ASPIRE participants use the ring more consistently. 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.

In addition to Dr. Baeten, HOPE is being led by Thesla Palanee-Phillips, Ph.D., M.Sc., of the Wits Reproductive Health and HIV Institute, South Africa, who also served as ASPIRE protocol co-chair; and Nyaradzo Mgodi, MBChB, MMed, from the University of Zimbabwe-University of California San Francisco in Harare.

HOPE will be conducted at former ASPIRE sites in Malawi, Uganda, South Africa and Zimbabwe. To help move toward a more "real world" delivery model, visits in HOPE will be monthly for the first three months, and then quarterly thereafter. 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.

ASPIRE, which took place between August 2012 and June 2015, was conducted in parallel with a second Phase III trial, The Ring Study, led by IPM. Primary results of both studies were reported at the Conference on Retroviruses and Opportunistic Infections (CROI) in February 2016; ASPIRE results were also published onlinein the *New England Journal of Medicine*. Across both studies, HIV risk was reduced by about one-third, meaning that one in three women who might have otherwise acquired HIV did not.

IPM will conduct a follow-on study called DREAM (Dapivirine Ring Access and Monitoring), or IPM 032, to provide the active dapivirine ring to women who participated in The Ring Study. DREAM begins this month.

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.

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.

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. This information will help researchers probe why ASPIRE found the ring did not provide statistically significant protection from HIV infection for women younger than 21 years. 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.

In addition to Dr. Brown, other authors of the abstract being presented at AIDS 2016 are Dr. Palanee-Phillips (Wits RHI); Mark Marzinke, Ph.D. (Johns Hopkins University School of Medicine); Craig Hendrix, M.D. (Johns Hopkins University School of Medicine); Charlene Dezzutti, Ph.D. (University of Pittsburgh); Lydia Soto-Torres, M.D. (National Institute of Allergy and Infectious Diseases, NIH); and Dr. Baeten (University of Washington), on behalf of the MTN-020/ASPIRE study team. The study team includes more than two dozen investigators from the MTN's affiliated trial sites, central laboratories and administrative units in the U.S., Malawi, South Africa, Uganda 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.

Provided by Microbicide Trials Network