Interim open-label study results suggest higher dapivirine vaginal ring use, lower HIV risk

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IPM's monthly dapivirine ring. Credit: Andrew Loxley

Interim data from a large open-label study of the monthly dapivirine ring have found increased product use compared to a previous Phase III study. In addition, modeling data suggest that women's HIV-1 risk in the open-label study, known as DREAM, was reduced by more than half.

Developed by the nonprofit International Partnership for Microbicides (IPM), the monthly ring slowly releases the antiretroviral (ARV) drug dapivirine and is currently under regulatory review. The ring is designed to provide women with a discreet and long-acting HIV prevention option.

The interim analyses of DREAM, announced today at the 2018 annual Conference on Retroviruses and Opportunistic Infections (CROI), showed an increase in ring use over its parent Phase III study, with more than 90 percent of women in DREAM using the ring at least some of the time. The interim analyses also suggest that the overall HIV incidence rate among women in the DREAM study is 54 percent lower than would be expected without use of the dapivirine ring based on statistical modeling. This finding has important limitations due to the lack of a placebo comparison group in the open-label study (meaning that all participants know they are using the active product).

Interim data from a parallel open-label study of the ring called HOPE, led by the US National Institutes of Health-funded Microbicide Trials Network (MTN), reported nearly identical results today at CROI.

"DREAM suggests so far that when women know that the dapivirine ring has helped lower HIV risk in clinical trials, they are more likely to use it and see higher levels of protection," said Dr. Zeda Rosenberg, founding chief executive officer of IPM. "We are encouraged by these interim findings because more than 35 years into the epidemic, women still lack the range of practical options they need to protect themselves against HIV."

Today's news builds on data presented at CROI 2016, which showed that the dapivirine ring was well-tolerated and reduced HIV risk by about 30 percent overall in two large Phase III clinical trials in Africa—The Ring Study, conducted by IPM, and ASPIRE, conducted by MTN.

Notably, open-label studies of oral pre-exposure prophylaxis, or PrEP, a daily pill to prevent HIV, have also shown increases in adherence and HIV risk reduction compared to earlier Phase III studies of theproduct. "We hope to see this same trend for the ring," said Rosenberg. Women continue to become infected with HIV at alarmingly high rates, especially in sub-Saharan Africa where nearly 60 percent of adults living with HIV/AIDS are women. If approved, the ring could expand women's options with the first long-acting HIV prevention method. A range of prevention products are needed—including condoms, daily PrEP, long-acting rings and other methods in development—because no single approach will meet all women's needs or get the epidemic under control.

"We are heartened to report that dapivirine ring use is increasing in the DREAM study as we keep working to support women to stay HIV-free," said Dr. Annalene Nel, IPM's chief medical officer, who is leading DREAM. "We thank women in the study, their families and communities for staying with us on this journey to find HIV prevention solutions that women at high risk can use on their own terms."

IPM holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson (J&J), designed to ensure that women in low-resource settings have affordable access to any dapivirine-based microbicide. J&J is also partnering with IPM on product access, lending resources and expertise as IPM prepares for the ring's potential roll-out.

The dapivirine ring is currently under regulatory review by the European Medicines Agency (EMA) through an Article 58 application. This procedure allows the EMA, in cooperation with the World Health Organization (WHO), to provide 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. Should the EMA

grant a positive opinion, IPM will seek WHO prequalification, which many national regulatory agencies in African countries consider in their regulatory reviews. IPM also plans to submit applications to the South African Health Products Regulatory Authority and the US Food and Drug Administration.

DREAM and HOPE are ongoing and similarly designed open-label studies that are providing the dapivirine ring to women who participated in the former Phase III ring trials in Africa—The Ring Study and ASPIRE, respectively—who test HIV-negative and are not pregnant. The studies are collecting additional safety data and information on how women use the ring now that they are aware it was shown to reduce HIV risk in the Phase III studies. DREAM began in July 2016 and is expected to complete participant follow-up by December 2018. HOPE began in August 2016 and is expected to complete in October 2018. Final results of both studies are expected in 2019.

About DREAM

DREAM (Dapivirine Ring Extended Access and Monitoring/IPM 032) is being led by IPM at six former Ring Study sites in South Africa and Uganda among 940 women ages 20-50. All women who participate in DREAM are followed for approximately 12 months. For the first three months, participants attend monthly study visits, where they receive a new ring at each visit. Study visits are then conducted quarterly, when participants can choose to take two rings to insert at home or return to a monthly visit schedule. These data will help researchers better understand what women's preferences for ring uptake and access might be in the real world. All women receive regular HIV testing and counseling, condoms, testing and treatment for sexually transmitted infections, and supportive adherence counseling.

Results: DREAM and comparison to The Ring Study

The interim analyses were conducted on data collected from the 900 women enrolled in DREAM as of September 2017.

Safety: The ring was found to be well-tolerated in DREAM with a safety profile similar to The Ring Study.

Adherence: Adherence to the ring is assessed by measuring residual dapivirine levels in used rings, which are returned at each study visit. Current methods are unable to determine the precise duration of ring use, but interim data from DREAM show an increase in used rings that indicated at least some use (ranging from intermittent to consistent use), up from 83 percent in The Ring Study to 96 percent in DREAM.

Risk reduction: DREAM data suggest a 54 percent reduction in HIV-1 risk using a statistical method called bootstrap sampling. From July 2016 to September 2017, an HIV-1 incidence rate of 1.8 percent was observed, compared to an incidence rate of 3.9 percent in a simulated placebo group, which was based on data from participants with similar characteristics in the placebo arm of The Ring Study. As noted, the lack of a contemporaneous placebo group in DREAM poses important limitations on its comparison to the placebo-controlled Ring Study, which should be considered when interpreting these results.

Methodology: Using the bootstrap sampling method, researchers calculated expected incidence rates by characterizing the age, location and presence of curable sexually transmitted infections among women at their time of enrollment in DREAM, and identified a sample of women with matching characteristics in the placebo arm of The Ring Study. That sampling was repeated 10,000 times to calculate an average expected incidence rate for a simulated placebo group in DREAM.

Next steps for dapivirine ring research

Research is planned to evaluate the ring's safety in pregnant and breastfeeding women in partnership with MTN. IPM is also partnering with MTN on the REACH study, which will begin later this year, to assess adherence to and preferences for the monthly dapivirine ring and daily oral PrEP among young women ages 16-21 in Africa—a group with some of the highest HIV infection rates globally. Phase III studies of the ring showed no efficacy among women ages 18-21, likely due to low product adherence. Studies of PrEP have seen similar adherence challenges among young women.

IPM is developing a three-month dapivirine-only ring that would offer women increased convenience and reduce annual costs, and a three-month dapivirine-contraceptive ring to simultaneously offer HIV prevention and contraception. Both rings entered first clinical trials, led by MTN, in 2017.

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Provided by IPM