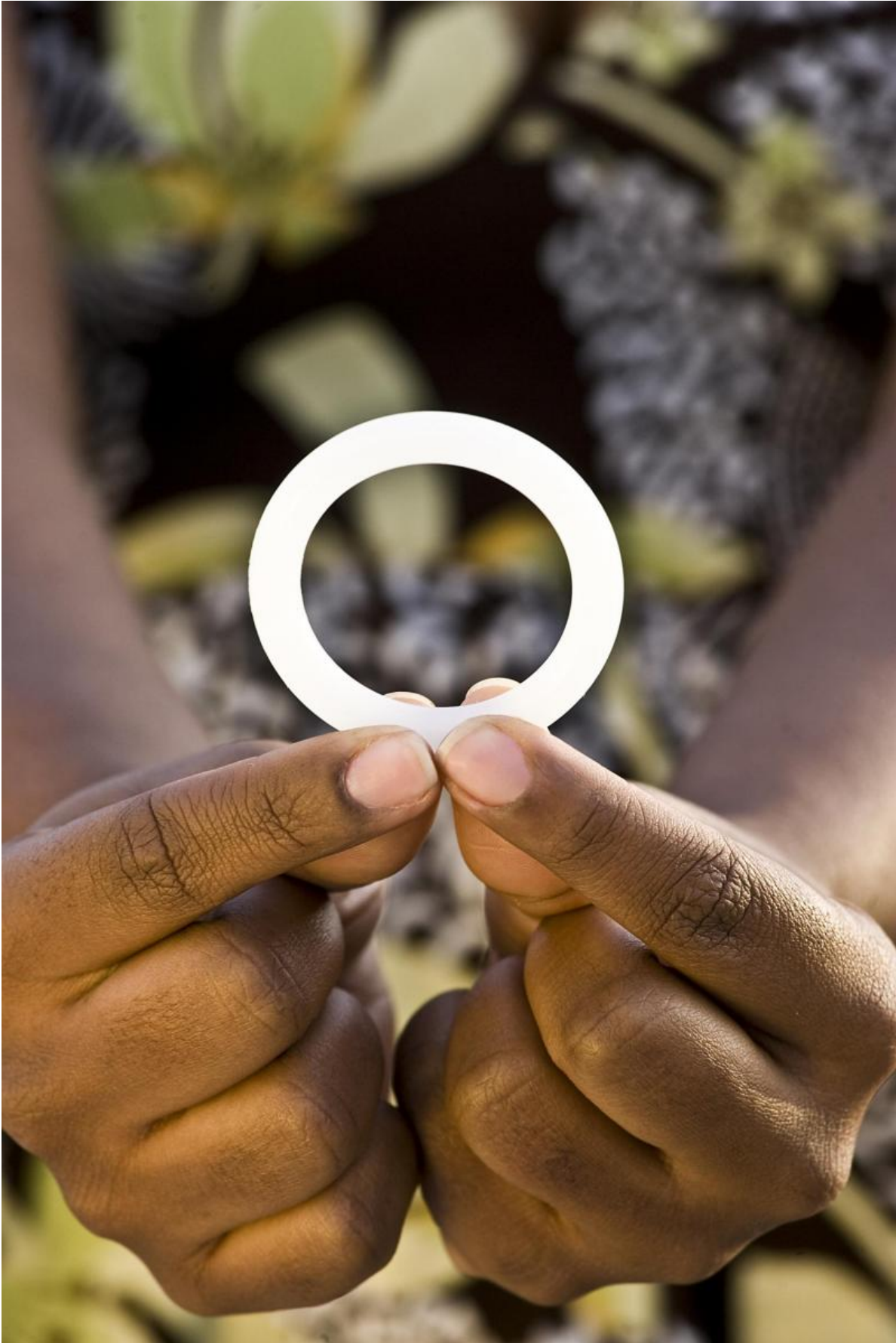


Dapivirine vaginal ring helped protect women against HIV in ASPIRE Phase III trial

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The monthly dapivirine ring, developed by the International Partnership for Microbicides. Credit: Andrew Loxley

A vaginal ring containing an antiretroviral (ARV) drug called dapivirine that women use for a month at a time was safe and helped protect against HIV in a large-scale clinical trial involving more than 2,600 women in Africa, researchers who conducted the trial, known as ASPIRE, reported today.

The study, which was led by the National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN), found the dapivirine ring reduced the risk of HIV infection by 27 percent overall - there were 27 percent fewer women who 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 risk of HIV was reduced significantly more among the study's older participants, who also used the ring most consistently. Women in the dapivirine group who were 25 and older were 61 percent less likely to acquire HIV than women of the same age in the placebo group. Intrigued with this finding, the researchers conducted 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 21 seeing their risk of HIV cut by more than half (56 percent).

ASPIRE enrolled HIV-negative women ages 18 to 45 at 15 clinical research sites in Malawi, South Africa, Uganda and Zimbabwe.

Results of the ASPIRE study were announced at the Conference on

Retroviruses and Opportunistic Infections (CROI) in Boston today, together with similar findings from a second trial of the dapivirine ring, two days ahead of their scheduled presentation. ASPIRE results were also published online today in the *New England Journal of Medicine*.

In the second trial, called The Ring Study, HIV risk was reduced by 31 percent overall, and by 37 percent among participants older than 21. The International Partnership for Microbicides (IPM), which developed the monthly dapivirine ring, is conducting The Ring Study in South Africa and Uganda among 1,959 women. Although still ongoing, The Ring Study is reporting results early, following a recommendation of its independent data and safety monitoring board that the study proceed to final analysis.

"This is a glass half-full moment," said Jared Baeten, M.D., Ph.D., of the University of Washington, who as protocol chair led the ASPIRE study. "The HIV prevention field for women has struggled in the last few years - at times the glass had seemed almost completely empty. Now, for the first time, we have two trials demonstrating that a female-controlled HIV prevention method can safely help reduce new HIV infections. I'm optimistic about what these results might mean for women worldwide."

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. While several studies have shown that ARVs are highly effective in preventing HIV, other studies - such as VOICE and FACTS 001 - suggest that for young, at-risk women in Africa, ARVs delivered as a vaginal gel or as a tablet may not be acceptable. Products must be used to be effective, and that was not the case for most of the participants in those previous studies.

Vaginal rings are flexible products that fit high up inside the vagina where they release a medication slowly over time. They are already used

in the United States and Europe to deliver hormonal contraception. Women can insert and remove the ring themselves. The dapivirine ring adapts that medical technology by using an ARV instead of contraception as a way to offer women potentially longer-acting protection against HIV.

ASPIRE was conducted between August 2012 and June 2015 and enrolled 2,629 women who were randomly assigned to use either the dapivirine ring or placebo ring for a month at a time throughout the study. Participation averaged 18 months, with some using their assigned monthly ring for up to 34 months. Women received a new ring at each monthly visit, plus condoms and HIV prevention counseling. They learned how to insert and remove the ring when they began the study and received additional guidance on its correct and consistent use throughout.

"Despite having never seen or used a vaginal ring, a number of study participants told us they were very comfortable inserting and removing the ring. A vaginal ring for HIV prevention can be used by African women. Expanding the number of HIV prevention options is important for women globally," said Thesla Palanee-Phillips, Ph.D., ASPIRE protocol co-chair who also directed the research site at the Wits Reproductive Health and HIV Institute (Wits RHI) in Johannesburg, South Africa.

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 reduction in HIV. 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, both pre-planned and post-hoc, found the reduction in HIV risk exceeded 50 percent in women older than age 21.

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.

"Our results make it all too clear that we must do more to address the unique needs of the youngest women in our study, who represent one of the highest-risk groups. Why didn't the ring work for them? We need to understand if it is adherence alone or biological or physiological factors. The blinded nature of the trial, with a placebo arm, also could have played a role, as we know from prior studies that some women may be nervous using a product before it is proven to be safe and effective," explained Dr. Baeten. In open-label studies of Truvada as oral pre-exposure prophylaxis (PrEP), both adherence and effectiveness were higher than in the original Phase III trials.

"Both ASPIRE and The Ring Study have raised important scientific questions about the susceptibility of very young women to HIV, as well as their willingness to use prevention products. Further research can address these knowledge gaps. With the number of new infections in women each year, time is not on our side. We cannot lose momentum in the search for products to reduce the spread of HIV," commented Sharon L. Hillier, Ph.D., of the University of Pittsburgh and principal investigator of the MTN.

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 to provide advice on the future of NIH-funded

dapivirine ring research.

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 studies are in preliminary stages. MTN-025, or HOPE, would gather additional data on the safety of and adherence to the dapivirine ring among former ASPIRE participants. 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.

"Ending the AIDS epidemic means focusing on women at greatest risk of HIV," said Zeda Rosenberg, Sc.D., chief executive officer of IPM. "Now that we know the dapivirine ring can help safely offer protection, IPM plans to seek regulatory approval and in parallel work with partners to better understand and build on today's findings. We hope this monthly ring will join other new innovations like oral PrEP as part of a comprehensive HIV prevention package that meets women's needs."

As sister studies, ASPIRE and The Ring Study were designed 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.

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 ring's development was made possible by a public-private partnership with 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.

More information: Results of both ASPIRE and The Ring Study will be announced in a press conference at CROI from 2-3 p.m. ET, Monday, Feb. 22.

Results of ASPIRE are detailed online ahead of print in *The New England Journal of Medicine*; the full manuscript and supplementary information are available at www.nejm.org/doi/full/10.1056/NEJMoa1506110

Provided by Microbicide Trials Network

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