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

Similar results are seen in second Phase III trial, The Ring Study

HARARE, February 22, 2016 –A vaginal ring containing an antiretroviral (ARV) drug called dapivirine that women inserted into their genital tract and used 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 Zimbabwe, Malawi, Uganda and South Africa, researchers who conducted the trial, known as ASPIRE, reported today.

[ASPIRE](#), which was led by the National Institutes of Health (NIH)-funded [Microbicide Trials Network \(MTN\)](#), enrolled HIV-negative women ages 18 to 45. In Zimbabwe, the study was led by [Dr Z. Mike Chirenje](#) of [University of Zimbabwe-UCSF \(UZ-UCSF\) Collaborative Research Programme](#). 678 women took part in the study across three clinical research sites in Harare and Chitungwiza, Zimbabwe.

The study 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. Researchers initially found that women in the dapivirine group who were 25 and older were 60 percent less likely to acquire HIV than women of the same age in the placebo group. Intrigued, they conducted additional analysis, which 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%.

Results of the ASPIRE study were announced at the [Conference on Retroviruses and Opportunistic Infections \(CROI\)](#) in Boston (USA) 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 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 an historic moment for us.” said Dr Chirenje, “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 in Zimbabwe and 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 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.

Contraceptive rings are already used in the United States and Europe to deliver hormonal contraception. These are soft, flexible products that are inserted high up inside the female genital tract where they release a medication slowly over time. Women can insert and remove the ring themselves. The dapivirine ring, which is also inserted high up inside the female genital tract, 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 this type of ring, the women who took part in the study told us they were very comfortable inserting and removing the ring. More importantly, the ring did not interfere with sex or menstruation” said Dr Felix Mhlanga, head of the Spilhaus Clinic Research Site in Harare.

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 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. 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 about using a product before it is proven to be safe and effective,” said Dr Chirenje. 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. The epidemic here in sub-Saharan Africa has a female face and with the alarming 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 in us African women” commented Dr Nyaradzo Mgodhi, ASPIRE Project Director at UZ-UCSF.

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 – all in the U.S. – 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. 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.

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ASPIRE and the MTN are funded by the U.S. National Institutes of Health grants UM1AI068633, UM1AI068615, UM1AI106707.

Results of ASPIRE and The Ring Study are being presented at CROI on Wednesday, 24 February and can viewed online approximately 24 hours later. Please go to www.croiconference.org for more information.

More 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

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>.

22-February-2016