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Sensitive ARV resistance tests detect no dapivirine-associated resistance among women using dapivirine vaginal ring in ASPIRE

New findings presented at HIVR4P 2018 suggest the risk is low that use of the dapivirine vaginal ring could result in virus becoming drug-resistant among women who acquire HIV

MADRID, October 24, 2018 – A monthly vaginal ring that slowly releases an antiretroviral (ARV) drug called dapivirine is currently undergoing regulatory review. If approved, the dapivirine ring would be the first biomedical HIV prevention method developed specifically for women. Importantly, it would also provide women with another option besides oral PrEP, which involves daily use of a tablet called Truvada. Oral PrEP is already approved and being rolled out in many countries.

Yet the concern with these and potentially any prevention method containing an ARV is that their use by someone who is unknowingly already infected could allow the virus to become resistant against the ARV and to other drugs in the same class, because while one ARV may be sufficient for preventing HIV, it is not enough to suppress the virus from continuing to replicate in someone who is infected. Moreover, if that individual were to infect others with drug-resistant virus, it would be increasingly more difficult to control HIV with mainstay drugs.

New findings reported today at the biennial HIV Research for Prevention conference (HIVR4P 2018) suggest the risk that drug resistance could develop with use of the dapivirine ring is minimal, though researchers caution that their results represent only one study.

The researchers, from the National Institutes of Health-funded Microbicide Trials Network (MTN), analyzed plasma samples from women who acquired HIV during participation in the ASPIRE Phase III trial using both standard genotyping and a more sensitive next-generation sequencing technique. Both tests identify changes, or mutations, in the genetic makeup of HIV that are known to cause resistance to certain drugs. Next generation sequencing, which is only being used in research settings, can target a specific region of a gene as well as detect mutations rarely seen with standard testing.

Among women who acquired HIV in ASPIRE, relatively few had evidence of resistant virus, particularly virus resistant to drugs in the same class as dapivirine, which are known as non-nucleoside reverse transcriptase inhibitors (NNRTIs). Moreover, the researchers did not find any rare mutations associated with resistance.

The results suggest that the few instances of NNRTI resistance were likely due to those women having been infected with drug-resistant virus and not due to the use of the dapivirine ring at the time of infection.

“We looked pretty hard, using the most sensitive tests that can detect genetic changes in thousands of individual viruses from a single infected person,” said Urvi Parikh, Ph.D., associate director of the Microbicide Trials Network (MTN) Laboratory Center Virology and Pharmacodynamics Core at the University of Pittsburgh. “In this study, we found that the risk of dapivirine-related resistance in someone using the dapivirine ring was the same as the risk in someone who wasn’t using the ring.”

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ASPIRE, which was conducted by the MTN, enrolled 2,629 HIV-negative women ages 18-45 at 15 trial sites in Malawi, Uganda, South Africa and Zimbabwe. The dapivirine ring, which is intended to be used for a month at a time, was developed by the nonprofit International Partnership for Microbicides (IPM). IPM also conducted The Ring Study, a sister Phase III study of the monthly ring with similar safety and efficacy results and is seeking regulatory approval of the ring.

Of the 2,629 women who participated in ASPIRE, 168 acquired HIV. Plasma samples from 165 women underwent testing for drug resistant virus using the standard genotyping technique (96 samples from women who had been assigned to use the placebo ring and 68 samples from women in the dapivirine ring group), while 123 samples were also tested using the more sensitive technique (61 from the placebo group and 62 from the dapivirine ring group).

Standard genotyping identified no differences in the frequency and patterns of HIV drug resistance between those assigned to use the monthly dapivirine ring and those assigned to use a placebo ring, with 8 of 69 (11.6 percent) of the dapivirine ring group and 10 of 96 (10.4 percent) of the placebo group having resistant virus.

Dapivirine resistance is most commonly associated with the presence of any of four specific mutations. Both tests yielded the same results, finding only two cases of NNRTI resistance among women in the dapivirine ring group who acquired HIV, each involving the same single mutation (K103N).

Looking at other common NNRTI mutations, the sensitive test uncovered only one case that had not been detected by the standard test. Finally, when researchers narrowed their search to the specific region of the gene where NNRTI mutations are most likely to exist, they found no significant differences in the type or frequency of mutations between the placebo and dapivirine ring groups.

“Dapivirine primarily stays in the vagina where it is needed to protect against HIV infection. Very little drug gets into the blood and goes elsewhere in the body. But should any HIV pass the drug barrier in the vagina and start multiplying in the bloodstream, there probably isn’t enough dapivirine circulating to be noticed and to cause resistant virus to emerge,” explained Dr. Parikh.

Truvada,® which contains the ARVs emtricitabine and tenofovir, is used for both HIV prevention and, in combination with other drugs, also for treating HIV. Dapivirine, on the other hand, has been developed exclusively for HIV prevention, although other drugs in its class of NNRTIs are used for treatment. Women who acquired HIV during ASPIRE immediately stopped using their assigned ring to avoid the possibility that the virus could become resistant to dapivirine or other NNRTIs, such as efavirenz and nevirapine, which are commonly used in treating HIV. Similarly, with PrEP, a person must test negative for HIV before starting the regimen and be tested regularly thereafter.

IPM holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen), which is designed to ensure that women in low-resource settings have affordable access to any dapivirine-based microbicide.

In all, 20 oral and poster presentations will be given by MTN investigators at HIVR4P 2018, which runs Oct. 22-25. Additional presentations include two plenary talks and a number of satellite sessions and conference symposia.

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Dr. Parikh will discuss her abstract, *Sensitive Next-generation Sequencing of HIV-1 From Seroconverters in the MTN-020/ASPIRE Dapivirine Vaginal Ring Study,* in an official HIVR4P press conference on Wednesday 24 Oct. from 12:00-13:00 CET. All press conferences will be live-streamed on the HIVR4P Facebook page and available for playback on the HIVR4P website. She will formally report the study’s results in Oral

Abstract Session 23 - Great Expectations: The Impact of PrEP, Thursday 25 Oct. from 10.30-12.00. HIVR4P sessions will be webcast and available on the conference website.

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For more information about the dapivirine ring, go to www.ipmglobal.org.

The 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.

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