

AVAC's Take

This issue of *Px Wire* gives readers a closer look at the dapivirine vaginal ring for HIV prevention. Data from two large-scale ring trials—ASPIRE and The Ring Study—were reported at CROI 2016 and... It works! Modestly. (More on that below.) “What’s next?” Read on for initial answers and some new questions. —AVAC

Data Dispatch: Dapivirine ring

What were the results?

In February 2016, results from two efficacy trials of monthly dapivirine vaginal ring use showed modest HIV protection. The two trials, known as ASPIRE and The Ring Study, showed overall protection of 27 percent and 31 percent respectively. There were important differences when efficacy was analyzed by age. The table in the centerspread provides more detail on the results.

Does a “modest” effect matter?

Yes. The two trials, which were independently conducted, had very similar positive results. This is the first time that two efficacy trials of a vaginal product have confirmed a positive finding. Data from two trials are generally required for approval of a product and these data should trigger regulatory review. The data show that, as with daily oral PrEP, the ring works when it is used correctly and consistently.

What happened with women under age 21?

The results from both studies show that protection differed by age and that younger women (under 21) were not protected. As measured in the trial, adherence was lower in these women. Young women in some trials of oral PrEP and vaginal tenofovir gel have also had very low rates of product use. Low use means low or no protection, and that is one explanation for the findings to date. However, there is a need to assess biological factors that may influence safety and efficacy of products in adolescents and young women.

Some of the issues to explore further in understanding younger women’s vulnerability to HIV infection include whether they may be at higher risk because they are having sex with partners who were recently infected and so have very high viral loads, lower condom use than slightly older

peers, possible age-specific biological vulnerability of the genital tract (e.g., ectopy that could indicate a larger surface area of vulnerable cells exposed) and more.

The Microbicide Trials Network (MTN) (which conducted ASPIRE) is planning a new study—MTN-034—to look at safety of and adherence to the dapivirine ring and TDF/FTC (Truvada) as oral PrEP among 450 young African women (16-21 years) at sites in South Africa, Uganda and Zimbabwe. It will also measure changes in the vaginal microenvironment during product use that might affect HIV risk, and look for biomarkers for safety and efficacy in mucosal secretions. The study also plans to compare the acceptability of daily oral PrEP to month-long use of the dapivirine vaginal ring.

Didn't these trials promise to solve adherence challenges?

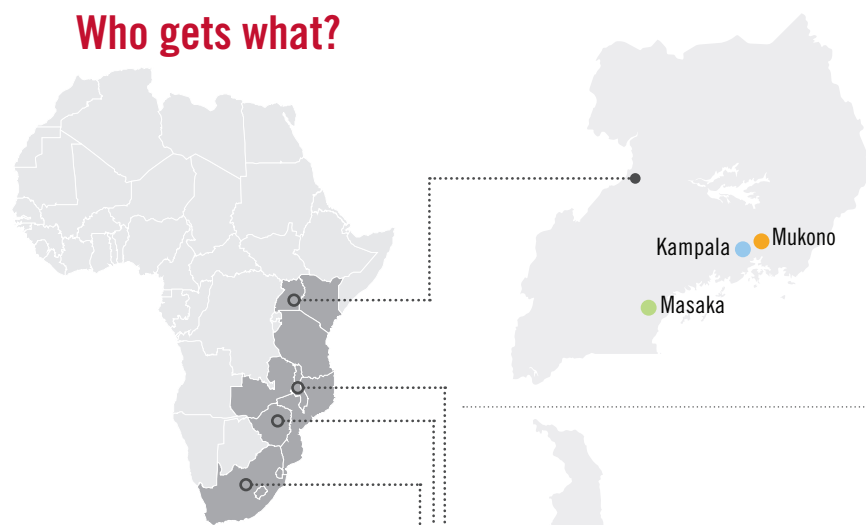
The ring trials were already underway when results from the VOICE study showed very low rates of adherence (based on analysis of blood samples) in many women in spite of high self-reported product use. Both the Ring and ASPIRE studies implemented a range of strategies to try to identify and address adherence issues in real time. Each study collected used rings from participants and analyzed the amount of drug left in the rings. This “residual drug level” was used to estimate whether women wore the ring consistently or not. They also checked drug levels of dapivirine in the blood. One lesson from the trials is that the residual drug levels originally selected as the threshold for adherence may have been too high. In other words, a woman could wear the ring for a few days—not enough for protection—and there would still be a residual drug level suggesting consistent use. However even with imprecise measurements of adherence, the trials were able to identify sites where adherence was a challenge and address issues proactively.

What else will we learn from the Ring and ASPIRE studies—and what will we not?

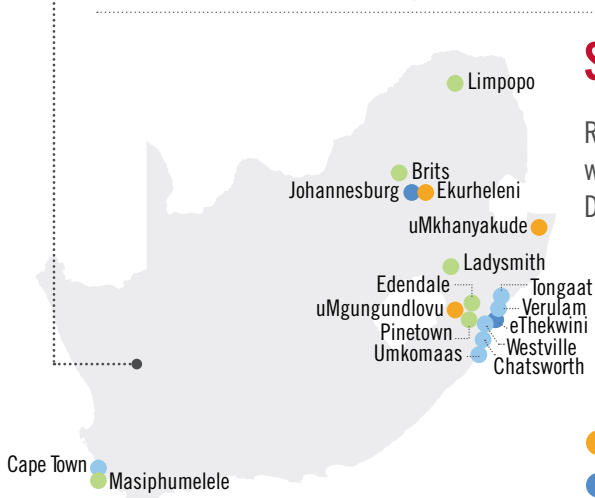
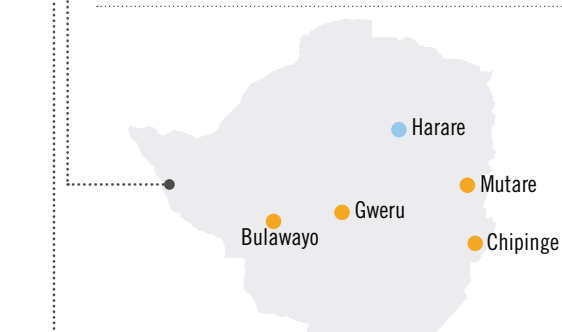
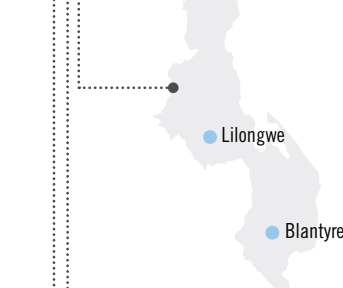
The information shared in February for both studies were only the topline results of effectiveness and safety. There are more data to analyze including on contraception choices, biological factors, adherence motivators and challenges. More presentations and peer-reviewed papers are forthcoming in 2016 and 2017. The open-label extension (OLE) studies (see back page) as well as any other follow-on studies will provide more information.

Patchwork of Prevention for Women: Oral PrEP and the Dapivirine Ring

Who gets what?



In the next 12 months, participants in the ring efficacy studies will get extended access to the ring via open-label studies. In three out of four of the countries where this is planned, PrEP is also rolling out for women—albeit in different districts or provinces. This means a lost opportunity to find out women's preferences and to introduce multiple prevention concepts at the same time. Specifically, South Africa, Uganda and Zimbabwe are all offering PrEP and continuing open-label trials of the ring. All three are offering PrEP via the PEPFAR DREAMS initiative. South Africa has a range of other PrEP projects for women underway. Only Malawi, which is host to ring OLEs, is unlikely to have any PrEP programming in that same timeframe. It's important to note that the PEPFAR DREAMS program is different from the planned DREAM open-label extension trial of the Ring.



Uganda

For now, the only PrEP access is via DREAMS-supported PrEP demonstration projects in 18-24 year-old female sex workers and other high-risk young women. Women in the ASPIRE trial will receive the dapivirine ring.

Malawi

Malawi is the one country where follow-on work for the dapivirine ring is planned in the same districts where DREAMS is operating. There is the opportunity to investigate women's preferences, but Malawi has no plans to implement PrEP for now.

Zimbabwe

DREAMS is providing support to expand PrEP access to sex workers, building on the ongoing SAPPH-Ire Study.

South Africa

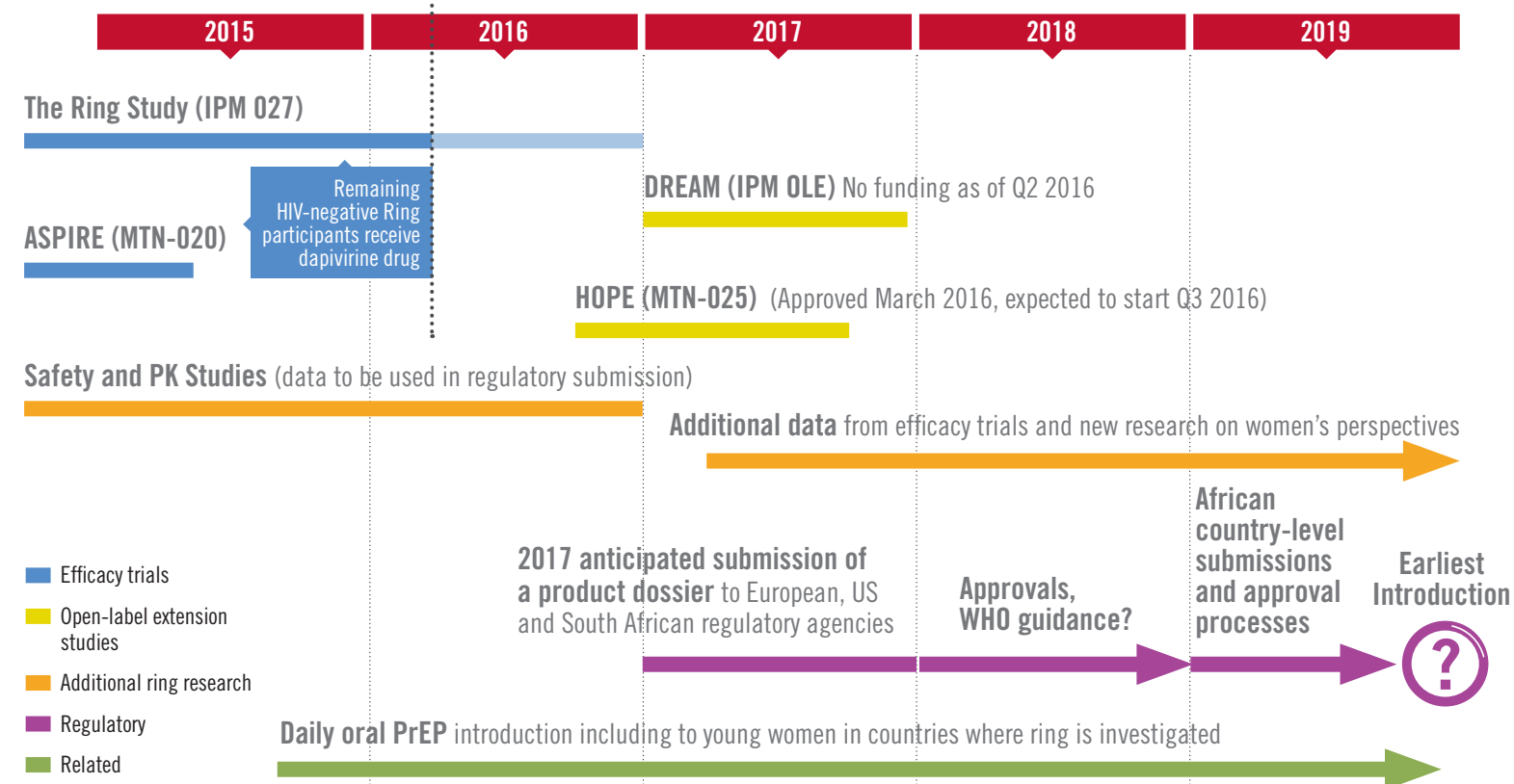
Rollout is starting with PrEP programs for sex workers, with a range of projects planned or underway both via DREAMS and other implementers.

- PrEP accessible sites
- HOPE sites where PrEP accessible
- HOPE sites without PrEP
- Potential DREAM OLE sites without PrEP (none where PrEP accessible)

Dapivirine Ring Results—A Snapshot

Study	The Ring Study (IPM 027) International Partnership for Microbicides	ASPIRE (MTN-020) Microbicide Trials Network
Study design and enrollment		
Objectives	Long-term safety and effectiveness	Safety and effectiveness
Study design	Double-blind randomized placebo controlled with 2:1 randomization (active: placebo)	Double-blind randomized placebo controlled with 1:1 randomization (active: placebo)
Enrollment	Total: 1959 women, ages 18-45; Active arm: ~1300	Total: 2629 women, ages 18-45; Active arm: ~1325
Regulatory requirement	3000 women on dapivirine ring for at least 1 year follow-up; 1500 women on dapivirine ring for 2 year follow-up	
Participant follow-up	2 years + 6 weeks following ring discontinuation	Minimum 1 year + 4 weeks following ring discontinuation
Research sites	7 IPM research center partners in South Africa and Uganda	15 MTN research centers in Malawi, South Africa, Uganda, Zimbabwe
Results		
Overall results	31% effective, confidence interval 1-51	27% effective, confidence interval 1-46
Secondary analysis that excluded data from 2 sites with lower retention and adherence		37% effective, confidence interval 12-56
Results by age stratification (post hoc analysis)		
Women over 21 years of age	37% effective, confidence interval 3.5-59	56% effective, confidence interval 31-71
Women 18-21 years of age	No statistically significant effect	No statistically significant effect
HIV incidence		
Overall	4.1% among women in active arm 6.1% among women in placebo arm	3.3% among women in active arm 4.5% among women in placebo arm

Results announced at CROI 2016



How do these data relate to previous ARV-based prevention research?

In previous trials of daily oral PrEP and 1% tenofovir gel, older women reported higher levels of adherence, as was also seen in the ring trials. Younger women in the trials used the products less frequently. This means that, in the trial context, the products did not work in young women's lives. Another common thread across these studies is very high incidence, 3–6 percent among ring trial participants and 4–9 percent in other ARV-based prevention studies—a sobering number in any context and even more so in a trial where women receive a comprehensive prevention package.

What else will happen in the next 12–18 months?

The dapivirine ring is different from daily oral PrEP in that it is an experimental product (oral PrEP uses an existing, widely used drug for HIV treatment). This means quantities are limited and that the product can only be made available in research study settings until it is approved. These are described below:

- ▶ International Partnership for Microbicides (IPM), the sponsor of the Ring Study, has approval from the South African Medicines Control Council to move remaining participants into the intervention arm of The Ring Study. This means that these participants will receive—and know they are receiving—the dapivirine-filled vaginal ring (no placebo). IPM is also waiting on funding and approval for its open-label extension study, DREAM. Once the DREAM study is a go, all Ring Study participants will be eligible to enroll in DREAM, and the Ring Study will close out.
- ▶ MTN has approval and funding from the National Institutes of Health (NIH) to move forward with an open-label extension (OLE) for ASPIRE, which is called HOPE (MTN-025). The protocol is now being revised and reviewed and the study should begin Q3 2016. OLE studies would give all HIV-negative Ring and ASPIRE study participants access to the dapivirine ring while the product is being reviewed for licensure.

Both research teams will be combining and analyzing the data further to understand the challenges to adherence and why the youngest women had low levels of protection. There is a suite of follow-up studies planned and ongoing to better understand various aspects of dapivirine ring use.

What kinds of things will the OLE studies be able to measure and explain?

Open-label studies provide the first glimpse of real-world patterns of use and acceptability. They do this because for

the first time people both know what they are getting and have information on product effectiveness, neither of which are possible in a blinded, placebo-controlled trial. It's also important to note that the OLE won't generate data on use in younger (under 21) women as the ASPIRE and Ring Study trial participants will all be over 21 by the time either OLE study begins.

An excellent example of OLE information comes from the iPrEx OLE study of daily Truvada as PrEP. The study, which ended in 2012, suggested that people with high rates of risk behavior self-selected to use PrEP and that those people had high levels of adherence. It provided more opportunities to measure drug levels in the blood and to link these to levels of protection. It also provided insights into approaches to increasing adherence.

The ring OLEs will shed light on how women use the ring now that data show it is safe and modestly effective. In addition to the OLEs there will be additional studies of the ASPIRE and Ring Study data related to behavior, risk and biology.

When will the dapivirine ring be available?

IPM, the ring's developer, plans to prepare and submit the "dossier of evidence," which regulators require to license the product for public use, in the first quarter of 2017. After that, it needs to be approved and, for many countries, WHO guidance and/or national approval is also a prerequisite. 2019 is a very optimistic timeframe for access (see timeline in centerspread for details).

What do advocates do in the meantime?

- ▶ Deliver what we have. Provide oral PrEP to women and men with substantial risk, as recommended by the WHO.
- ▶ Advocate for full funding of the DREAM open-label extension and related studies.
- ▶ Broaden and sustain the pipeline. Research into long-acting injectables, vaccines, vaginal and rectal microbicides, multipurpose prevention options and broadly neutralizing antibodies must also continue.

About AVAC



AVAC works to accelerate the development and global delivery of HIV prevention tools. To receive regular updates via email sign up at www.avac.org/signup.

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