HIV Protection, Birth Control Levels Vary in Studies of Vaginal Rings

To date, no head-to-head trial has compared the prevention methods.

February 3, 2021 By Heather Boerner

This article has been updated to reflect additional information and for clarity.

Separate trials of vaginal rings for HIV and pregnancy prevention found that levels of topical dapivirine and tenofovir drop at different rates during periodic removal, according to data presented at the 4th HIV Research for Prevention virtual conference.

In a trial of a 90-day vaginal ring loaded with dapivirine, levels of the drug in vaginal fluid dropped "precipitously" during periodic removal. Meanwhile, the drops were not as steep in rings loaded with tenofovir, even when the rings were removed for an extra day.

What this will mean for HIV protection is unclear. The trials were early safety studies and so did not assess whether the differing drug levels were associated with differing rates of HIV acquisition. Such trials are under development.

The studies were among the first to test flexible silicone rings designed to protect against both pregnancy and HIV. For birth control, both contained levonorgestrel, the hormone in the Mirena intrauterine device. The rings loaded with tenofovir are also being tested as protection against herpes simplex virus.

The hope with multipurpose prevention technology like the rings is that women may be more motivated to keep them in for their contraceptive benefits—and therefore reap more protection against HIV—than if they were HIV preventive rings alone. This is important because open-label studies of a 30-day dapivirine ring found that among women who used the ring at all, HIV acquisition dropped by an average of 50%. But that was among all women who received the rings. Protection likely is higher among women who use them more.

If the rings prove effective, they could eventually join injectable cabotegravir as long-acting prevention methods for women. Neither is yet approved for use by the Food and Drug Administration.

Tenofovir/Levonorgestrel

In the ENRICH trial, led by CONRAD, 47 women in Norfolk, Virginia, and in Santo Domingo, Dominican Republic, were randomized to one of four arms: to use the tenofovir/levonorgestrel ring continuously for 90 days, to use the ring on 28-day cycles or to use placebo rings for both lengths of time. Five participants received the placebo for each time schedule.

Tenofovir has never been tested as a vaginal ring before, though there have been studies looking at tenofovir gels for vaginal HIV prevention.

Fourteen women completed the continuous arm, and 16 completed the 28-day arm. At the end of the five-month study period, the most common treatment-associated adverse events included mild to moderate upper respiratory tract infections, influenza, vaginal discharge and nausea. In addition, the ring wasn't associated with any significant changes in the menstrual period.

Tenofovir diphosphate levels in vaginal fluid rose to above target levels by 48 hours after insertion and remained above those levels, even during the three days when women on the 28-day cycle arm removed the rings. The researchers found levels of tenofovir above target levels in vaginal tissue, as well.

But the tenofovir ring contained less levonorgestrel than the dapivirine ring—a so-called "micro-dose." So when women removed the tenofovir ring, levels of the contraceptive dropped further than they did with the dapivirine ring.

A companion trial of tenofovir rings with and without levonorgestrel in women in Kenya found that the primary treatment-related adverse events were related to bleeding. In addition, one woman found that the ring repeatedly became dislodged and fell out.

Dapivirine/Levonorgestrel

The results in the dapivirine/levonorgestrel ring study showed higher levels of the contraceptive when the rings were removed, but lower levels of dapivirine.

Like the tenofovir ring trial, the Microbicide Trials Network 030 study enrolled women in a continuous-wear group for 90 days and a periodic removal arm for cyclic removal for two days every 28 days. The trial, which recruited 25 women in Pittsburgh, did not include a placebo arm.

Ninety percent of participants completed the 90-day trial with no significant difference between the arms. Surprisingly, said Sharon Achilles, MD, of the University of Pittsburgh, who presented the data, there were high rates of ring slippage and spontaneous ring expulsion: 76% experienced slippage, and 40% experienced expulsion across arms. This was a result, said Achilles, of the increased dosage of levonorgestrel. The ring has been reformulated with the same amount of contraceptive in a slightly different form to address the issue. Trials of that combination are forthcoming.

When the ring was in, levels of both the HIV and pregnancy prevention drugs were above target levels. Median plasma dapivirine concentrations, for instance, were at or above 500 picograms per

milliliter for both continuous and cyclical use—far above the 300 pg target level thought to protect against HIV. And levonorgestrel plasma levels were well above the 200 to 300 pg levels necessary to protect against pregnancy.

“With cyclic removal, there is the expected drop in plasma concentrations” for both drugs, Achilles said.

Compared to absolute levels of levonorgestrel with the tenofovir ring, levels of the contraceptive remained higher when the dapivirine ring was removed. But when researchers looked at dapivirine levels, the drop in fluid concentration levels was “precipitous.”

“Dapivirine concentrations drop from nearly 100,000 nanograms per gram to about 10 ng per gram over hours, not days,” Achilles reported—which led researchers to wonder what effect this would have, if any, on HIV protection from the ring.

And this points to a basic science question that researchers studying topical prevention drugs are answering as they study the drugs themselves in women: How do you determine how effective a topical, rather than a systemic, HIV prevention method is? With systemic prevention like Truvada or Descovy, the presence of drug throughout the body means that researchers can easily test whether concentrations are high enough to provide protection by examining blood or hair samples. For a topical drug designed not to impact the entire system, that’s not as easy.

“We do not know if it’s dapivirine concentrations in vaginal fluid, or tissue, or plasma that will be critically important for the ability of dapivirine to prevent sexual transmission of HIV,” Achilles said. “So this may be a concern for allowance of periodic removals of such [multipurpose prevention technology] products.”

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