Implants and Inserts Could Offer New HIV Prevention Options

An islatravir implant could potentially prevent HIV for several years, while an antiretroviral insert could offer on-demand protection.

April 3, 2023 By Liz Highleyman

Small implants placed under the skin and vaginal or rectal microbicide inserts could potentially offer convenient new options for HIV pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), according to study results presented at the 30th Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle.

One research team tested a refillable islatravir implant that could last for several years, while another team evaluated a biodegradable implant. Both protected female monkeys against vaginal infection with an HIV-like virus, and the refillable implant also protected male monkeys against rectal infection. Other researchers showed that fast-dissolving rectal or vaginal tablet inserts containing elvitegravir and tenofovir alafenamide (TAF) appear promising for on-demand protection.

Daily or on-demand oral PrEP using tenofovir disoproxil fumarate/emtricitabine (Truvada or generic equivalents) or tenofovir alafenamide/emtricitabine (Descovy) and cabotegravir injections (Apretude) administered every other month are highly effective at preventing HIV. But PrEP uptake has been limited so far, and longer-acting or short-term methods could offer attractive alternatives for some people.

“We need to increase PrEP access by providing multiple options to have better persistence and adherence,” Alessandro Grattoni, PhD, of the Houston Methodist Research Institute, said at a CROI media briefing.

Islatravir Implants

Long-acting injectable PrEP has the drawback of waning drug levels over time, and the drug cannot be removed in case of medical complications. Long-lasting implants placed under the skin, usually on the upper arm, could overcome these limitations. What’s more, many women are already familiar with implants for long-acting contraception.

An earlier islatravir implant developed by Merck contained enough of the drug to provide protection for at least a year. That implant demonstrated favorable pharmacokinetics and safety in

an early human study presented at CROI 2021, but its current status is unclear. However, continued use would require repeated minor surgical procedures to remove the old implant and replace it with a new one; this would not be necessary if an implant could be refilled.

Grattoni and colleagues developed an implant based on nanofluidic silicon membrane technology. The experimental implant, which is about an inch long, has two ports. To refill it, one needle is inserted through the skin to fill the first port, while another needle is used to withdraw excess fluid from the second port. Grattoni said the procedure could be done by a trained nurse.

In a pharmacokinetic study, implants were inserted under the skin on the back of macaque monkeys, and drug concentrations were measured over time. The implant produced sustained islatravir release in both male and female animals. Steady islatravir blood levels, above those established for PrEP protection, and islatravir triphosphate (the active form of the drug) levels in cells were maintained for more than 20 months. The implants were generally well tolerated, producing mild local tissue inflammation but no signs of systemic toxicity. There were no notable adverse events even at high doses, Grattoni reported.

Next, the animals were challenged with repeated low doses of SHIV, a hybrid simian-human virus. Six male monkeys received 10 once-weekly rectal exposures, while six females received the same number of vaginal exposures. None of the monkeys with islatravir implants were infected, leading the researchers to conclude that the implants "conferred 100% protection against rectal and vaginal infection." In contrast, all control monkeys who got inactive placebo implants were infected.

In a second study, Michele Daly, PhD, of the Centers for Disease Control and Prevention (CDC), and colleagues evaluated islatravir implants made of polycaprolactone, a biodegradable polymer. Daly noted that islatravir could potentially be combined with contraceptives in the same implant, and the implant has also been tested with TAF. Although a biodegradable implant would need to be replaced periodically if an individual wishes to continue using the method, it might not need to be removed if someone wanted to stop.

Here, six female macaques received two implants, one under the skin of each upper arm. After five weeks of pharmacokinetic monitoring, they were vaginally exposed to SHIV twice weekly for six weeks. Next, one implant was removed, after which they were monitored for another five weeks and then repeatedly exposed to SHIV again. Islatravir levels were higher with two implants but remained adequate even with one. Plasma concentrations were similar to those seen with once-daily oral doses of islatravir in humans. Again, the implants were well tolerated, and most animals did not have implant site reactions.

None of the six monkeys became infected after 12 SHIV exposures while they had two implants. After one implant was removed, one of the six animals became infected. The breakthrough infection was detected six weeks after the last SHIV exposure, and this monkey had the lowest islatravir blood level. Two animals with placebo implants and four with no implants were infected.

While these findings are promising, the fate of islatravir remains unclear. In December 2021, trials

of islatravir for HIV treatment were put on a partial clinical hold, and PrEP trials were put on a full hold after HIV-positive study participants experienced declines in CD4 T-cell counts and HIV-negative volunteers saw decreases in total lymphocyte counts. Last September, Merck announced that it would start new treatment trials using lower doses of islatravir, but islatravir PrEP would be discontinued. Discussing the drug's effect on lymphocytes, Kathleen Squires, MD, of Merck, said the company is "looking at possibilities" for implants.

Rectal and Vaginal Inserts

Research on microbicides has slowed since the advent of oral and injectable PrEP, but a short-term method that can be used before or after sex could be a welcome option for some people.

Sharon Riddler, MD, of the University of Pittsburgh, and colleagues conducted a Phase I study (MTN-039) of a rectal tablet insert containing Gilead Sciences' integrase inhibitor elvitegravir and TAF. The fast-dissolving tablet is small and discrete and can be self-administered, Riddler noted.

Fast-dissolving microbicide insertCONRAD

Gustavo Doncel, MD, PhD, the scientific and executive director CONRAD, a nonprofit prevention research organization, explained that development of the microbicide started awhile ago, before

Gilead's newer integrase inhibitor, bictegravir (a component of Biktarvy), was available. He added that although oral elvitegravir (part of the Stribild and Genvoya coformulations) requires a booster, this is not the case for topical administration.

Previous research showed that one elvitegravir/TAF insert partially protected monkeys against SHIV rectal exposure, with an efficacy of 73%, rising to 93% when two inserts were used together.

In this first human study, 23 HIV-negative volunteers (17 men and six women) used a single insert, and then, after a seven-day washout period, used two inserts. Blood, rectal fluid samples and rectal tissue biopsies were collected for drug level measurements for up to 72 hours after the inserts were administered.

Drug levels were higher—but not twice as high—when participants used two inserts versus one. Elvitegravir and tenofovir were detectable in rectal fluid samples by two hours after administration. Elvitegravir fell below detectable levels by 24 hours, but tenofovir remained measurable for 72 hours. Tenofovir diphosphate levels in rectal tissue cells remained above protective levels—and usually higher than those seen in people taking oral PrEP—for 48 hours with a single insert and 72 hours with a double dose. When rectal tissue was exposed to HIV in the laboratory, levels of the p24 antigen, produced when the virus replicates, were significantly reduced. The inserts were safe and well tolerated.

These results indicate that the elvitegravir/TAF insert "has great potential as an on- demand rectal microbicide for HIV prevention," the researchers concluded.

The insert also shows promise for vaginal use. Natalia Makarova, of the CDC, and colleagues, working with CONRAD, previously found that the insert was safe, well accepted and showed good pharmacokinetics in an early human trial. They also showed that the insert fully protected macaques when administered as PEP four hours after vaginal SHIV exposure and had 91% efficacy when used as PrEP four hours before exposure. In this study, they sought to define the window of protection.

Female monkeys were vaginally exposed to low-dose SHIV once weekly for 13 weeks. After each challenge, 12 animals received elvitegravir/TAF inserts eight or 24 hours later. Another nine monkeys received inactive placebo inserts or no inserts.

Only one of the six monkeys who received the inserts as PEP eight hours after exposure was infected, meaning the microbicide had 94% efficacy. But when the window was extended to 24 hours, three of six became infected, decreasing efficacy to 77%. The monkeys in the control group became infected after a median of three exposures.

"On-demand HIV prevention modalities used before or after vaginal sex may be a desirable alternative to daily oral pre-exposure prophylaxis for women with infrequent or clustered sexual activity," according to the researchers.

Click here for more news about PrEP.

Click here for more reports from CROI 2023.
