Are Cabotegravir Injections More Tolerable Than Lenacapavir?

Small study suggests cabotegravir shots cause fewer injection-related side effects, but they need to be taken three times more often.

October 20, 2025 By Liz Highleyman

HIV-negative people and healthcare providers found a single injection of cabotegravir more acceptable than lenacapavir shots in a small study presented at the European AIDS Conference in Paris. Cabotegravir is administered every other month versus every six months for lenacapavir, however, so time will tell how the two options stack up with longer use.

Cabotegravir, from ViiV Healthcare, and lenacapavir, from Gilead Sciences, are two long-acting injectable options for HIV treatment and prevention. Cabotegravir is sold alone under the brand name Apretude for pre-exposure prophylaxis (PrEP), and cabotegravir plus rilpivirine are sold together as Cabenuva for HIV treatment. Lenacapavir is sold alone as Yeztugo for PrEP and as Sunlenca for use in combination therapy for people with multidrug-resistant HIV.

For HIV prevention, clinical trials showed that cabotegravir is highly effective for cisgender men and transgender women who have sex with men (HTPN 083) and for cisgender women in Africa (HPTN 084). Likewise, lenacapavir PrEP offered excellent protection for African women (PURPOSE 1) and for gay and bisexual men and gender-diverse people (PURPOSE 2).

Given that both drugs work very well and are similarly priced, the choice of which to use may come down to convenience and side effects.

Cabotegravir is administered every other month as a single intramuscular injection, usually given in the buttocks. Injection-site reactions, such as pain, redness and swelling, were common in clinical trials, but these were mostly mild or moderate, decreased over time, and few participants stopped the drug for this reason.

Lenacapavir, in contrast, involves two subcutaneous injections administered together twice yearly, typically in the abdomen or thigh. It forms a depot in the fat layer under the skin that slowly releases the drug. In addition to pain, redness and swelling, lenacapavir can also form a hard nodule or lump where the drug is stored, which shrinks in size over time. Injection-site reactions and nodules were frequently reported in trials, but here, too, they were usually mild or moderate and rarely led to discontinuation.

The Phase I CLARITY trial (NCT06970223), sponsored by ViiV, is the first head-to-head comparison of the acceptability and tolerability of cabotegravir and lenacapavir injections. This open-label crossover study included 63 healthy HIV-negative participants. About two thirds were men, 62% were white, 29% were Black and the median age was 48 years.

The study participants were randomly assigned to receive a single dose of cabotegravir (one shot) or lenacapavir (two shots). They reported injection site reactions and their acceptability after seven days using a questionnaire. At Day 15, they received a single injection of the other drug and again reported their reactions. The incidence, severity and duration of injection-site reactions, as well as imaging, will be assessed over six months of follow-up. Seven health care providers also completed questionnaires about their preferences.

Most participants—about 80%—reported pain after both cabotegravir and lenacapavir injections. Other reactions, however, were more common after lenacapavir shots, including induration (87% versus 18%), nodules (74% versus 33%), swelling (58% versus 34%) and redness (57% versus 12%). Overall, there were about four times more injection-site reactions with lenacapavir, and participants were substantially more likely to have visible reactions after lenacapavir shots. As seen in the pivotal trials, most injection-site reactions were rated as mild or moderate. Less than 10% of participants reported severe reactions, there were no serious adverse events, and no one discontinued either cabotegravir or lenacapavir due to drug-related adverse events.

After receiving a single dose of each drug, 69% of participants said they found cabotegravir injections “very” or “totally” acceptable, compared with 48% who said the same about lenacapavir shots. Most (90%) said they preferred cabotegravir, while 10% preferred lenacapavir.

The most common reasons for preferring cabotegravir were less pain during injection administration, less post-injection pain or soreness, shorter duration of injection-site nodules or swelling and smaller nodules or swelling. The most common reasons cited by those who preferred lenacapavir were similar: less pain or soreness after injections, duration of nodules or swelling, size of nodules or swelling and fewer side effects. These findings show that individual experience can vary considerably.

Of the seven surveyed health care providers, six (86%) preferred cabotegravir while one preferred lenacapavir. Those who favored cabotegravir cited fewer side effects, less severe injection-site reactions and less pain during injections. The provider who preferred lenacapavir cited the ease of injection preparation.

Real-world experience often differs from outcomes in clinical trials. Apretude was approved for HIV prevention in late 2021, but it is still not widely used. In part, this is due to administration logistics, cost and difficulties with reimbursement, but some people have stopped cabotegravir PrEP because the shots are painful. Yeztugo PrEP was approved this past June and real-world use remains limited.

Even if lenacapavir causes more or worse injection-related side effects, being able to take shots twice rather than six times a year may be an acceptable trade off for some people. These study

findings underscore the importance of individual choice and informed decision-making when choosing long-acting injectables for HIV prevention or treatment, according to ViiV.

“We believe long-acting innovations will play a critical role in the global response to ending HIV and AIDS, and understanding potential differences in acceptability and tolerability of options is an important consideration when choosing between long-acting injectables,” ViiV chief medical officer Jean van Wyk, MBChB, said in a news release. “These early findings provide valuable insights into long-acting injectable options to help empower individuals and their healthcare providers to make fully informed choices.”

Click here for more news about HIV prevention.
Click here for more news from EACS 2025.
