Could Cabenuva and Apretude Injections Be Self-Administered?

New formulations and alternative injection sites could allow people to administer the shots at home.

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A high-concentration formulation of long-acting cabotegravir and alternative injection sites such as the thigh or belly could potentially allow people to self-administer Cabenuva for HIV treatment or Apretude for pre-exposure prophylaxis (PrEP), according to a pair of studies presented at the 24th International AIDS Conference in Montreal. This could help overcome one of the major barriers to wider adoption of long-acting injectables.

One research team showed that a high-concentration formulation of injectable cabotegravir had similar safety and produced drug levels comparable to those of the current version. Another team found that injecting cabotegravir and rilpivirine into the thigh muscle led to mostly mild side effects and a pharmacokinetic profile comparable to butt injections.

Injectable cabotegravir and rilpivirine, sold together as Cabenuva, is the first complete antiretroviral regimen that does not require daily pills. Injectable cabotegravir alone, sold as Apretude, was approved last year as the first long-acting PrEP option.

Cabenuva currently involves two separate intramuscular injections in the buttocks administered by a health care provider either every month or every two months. Apretude is always given every other month. The shots contain a relatively large volume of liquid compared with, say, a typical vaccine.

Two Phase III clinical trials showed that Cabenuva leads to sustained viral suppression. The ATLAS study evaluated the regimen as maintenance therapy for treatment-experienced people who had a stable undetectable viral load while the FLAIR study enrolled previously untreated people. Two other trials, HPTN 083 and HPTN 084, showed that Apretude is even more effective than daily PrEP pills for HIV prevention.

Participants in these studies generally expressed a high level of satisfaction with the injections and said they preferred them over daily pills. Advantages of long-acting injections include not having to think about HIV treatment or prevention every day, not having pill bottles that could reveal one's HIV status or risk and, for some, better adherence. But HIV-positive people using Cabenuva

must visit a health care provider six or 12 times a year, more often than those on a stable oral regimen require viral load monitoring. And HIV-negative people using Apretude must see a provider for injections six times a year, more often than the quarterly monitoring recommended for people taking oral PrEP.

High-Concentration Cabotegravir

In the first study, Paul Benn of ViiV and colleagues evaluated the safety, tolerability and pharmacokinetics (PK) of a high-concentration formulation of long-acting cabotegravir in healthy HIV-negative volunteers. The 88 participants had a median age of approximately 34 years and about 40% were women. Fourteen people (16%) had a body mass index classified as obesity.

Currently, people taking monthly Cabenuva receive 400 milligrams of cabotegravir plus 600 mg of rilpivirine every four weeks, while those on the every-other month schedule get 600 mg of cabotegravir—also the dose used for PrEP—plus 900 mg of rilpivirine every eight weeks. However, the monthly injections come in 2-milliliter vials while the every-other-month shots come in 3-milliliter vials, so the actual cabotegravir dose is 200 mg/ml in both cases.

The experimental high-concentration cabotegravir formulation is 400 mg/ml, meaning twice as much active drug per volume. It was developed to support less frequent dosing or potential self-administration via subcutaneous (under the skin) or thigh injections. This study looked at long-acting cabotegravir only; for self-administered treatment, a more concentrated formulation of rilpivirine might also be needed.

After a 28-day oral lead-in period on cabotegravir pills, four cohorts received two once-monthly injections containing various doses (200 to 600 mg) of the 400 mg/ml formulation administered either as an intramuscular injection in the buttocks or outside of the thigh or as a subcutaneous injection in the abdomen. A fifth cohort received a single larger dose (800 mg) in the buttocks to explore the potential for administration once every three months. In each cohort, some participants received the standard 200 mg/ml formulation for comparison.

The AIDS 2022 poster described various PK parameters including maximum drug concentration, trough concentration (lowest level between doses), concentration at four weeks, terminal half-life (the time for the concentration to fall to half its original level) and absorption rate.

Overall, dose-normalized PK parameters for the 400 mg/ml formulation were similar across all dose levels and administration routes. However, the half-life was about 60% shorter and the absorption rate was 160% higher compared with the standard 200 mg/ml formulation. That is, the high-concentration formulation was absorbed faster, resulting in a shorter half-life, according to the researchers. Administration every four weeks resulted in plasma drug concentrations within the range seen with the standard formulation, but longer intervals would require a high dose volume the researchers deemed impractical.

Most participants experienced injection site reactions such as pain, swelling, induration or redness, but these were usually mild and transient. Swelling, induration (hardness) and nodules were more common after subcutaneous abdominal administration compared with intramuscular shots.

Reported pain scores were highest five days after an injection. Scores were somewhat higher for thigh or abdominal injections compared with buttocks injections, but the researchers cautioned that the numbers were small. Despite injection pain being common, most participants ranked it as only a little bothersome and most considered it acceptable.

Other types of adverse events were uncommon. Twelve people had severe (Grade 3) side effects, and five people discontinued the study after the first injection for this reason. Overall, the researchers concluded that the safety profiles of the high-concentration 400 mg/ml formulation and the standard 200 mg/ml formulations were similar.

Based on these findings, Benn's team concluded, the 400 mg/ml formulation of cabotegravir "could potentially expand options for long-acting injectable antiretroviral therapy, and these interim safety and PK data support further clinical evaluation."

Cabenuva Thigh Injections

In the second study, Kelong Han, PhD, of GlaxoSmithKline (ViiV's parent company) and colleagues evaluated the pharmacokinetics and tolerability of Cabenuva administered in the outer thigh rather than the buttocks. This could allow for self-administration and offer an alternative injection site in cases where butt injections are unfeasible or intolerable.

The study included 15 healthy HIV-negative volunteers, six of whom were women; one withdrew early due to pregnancy. The median age was 33 years, and white and black people were equally represented.

After an oral lead-in period using cabotegravir and rilpivirine pills, participants received 600 mg of cabotegravir and 900 mg of rilpivirine—the standard doses when using the every-other-month schedule—administered in the lateral thigh muscle (vastus lateralis). Follow-up data were collected for a year.

The researchers looked at PK parameters including maximum drug concentration, trough concentration, concentration at four weeks and "area under the curve," a measure of total drug exposure. After thigh injections, the participants had drug concentrations well above active levels and within the range seen with buttocks injections.

Again, injection site reactions were common. But other side effects, such as chills, headache and insomnia, were uncommon, and there were no serious adverse events. All participants reported injection site pain, and about half reported induration or swelling. These were usually mild (79%) or moderate (15%) and lasted a median of eight days. The researchers noted that the level of pain was higher soon after rilpivirine injections compared with cabotegravir injections.

These findings "support further evaluation of thigh intramuscular injections in target populations," they concluded.

Although implementation studies have found that patients and providers can adapt to regular

injection visits, uptake of long-acting Cabenuva for treatment and Apretude for PrEP have been low so far. Enabling people to give the shots themselves at home could make these options more attractive.

Click here to read the high-concentration cabotegravir abstract.

Click here to read the Cabenuva thigh injection abstract.

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