Innovative Use of Long-Acting Injectables Holds Promise for People with Adherence Challenges

Cabenuva for people without viral suppression and long-acting cabotegravir plus lenacapavir may be options for people who can't take daily pills.

March 20, 2024 By Liz Highleyman

Antiretroviral treatment using cabotegravir and rilpivirine injections (Cabenuva) can be an effective HIV treatment option for people who have trouble maintaining viral suppression on daily pills due to adherence challenges, according to studies presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2024) in Denver.

One trial gave people intensive support to achieve viral suppression on a daily oral regimen before switching to Cabenuva, in accordance with the current label indication. Another study started the injections directly for people who had difficulty taking pills consistently. In addition, a case series suggests that injectable cabotegravir plus lenacapavir (Sunlenca) may also be a feasible option.

"The HIV community is just beginning to unpack the enormous potential of long-acting antiretroviral medications for HIV treatment and prevention, and we need population-specific data for everyone to benefit," National Institute of Allergy and Infectious Diseases director Jeanne Marrazzo, MD, MPH, said in a news release. "These findings open up new possibilities for millions of people with HIV, particularly those whose health suffers due to challenges of daily pill taking."

Injectables After Pills

All modern antiretroviral therapy (ART) is highly effective and generally well tolerated, so treatment success often comes down to consistent use. Some people have difficulty maintaining good adherence because they forget to take their pills, don't want to think about HIV every day, are concerned about having pill bottles that could reveal their HIV status or are in living situations where their meds could be lost or stolen. About a third of people with diagnosed HIV in the United States do not have viral suppression, which means they are at risk for disease progression and could transmit the virus to others.

For some of these individuals, long-acting treatment may be a better option. Approved in 2021,

Cabenuva is the first complete antiretroviral regimen that does not require daily pills. The treatment involves two injections administered by a health care provider once monthly or every other month. Cabenuva is approved for people with viral suppression on a stable antiretroviral regimen, no history of treatment failure and no resistance to either drug. (Injectable cabotegravir alone, sold as Apretude, is approved for HIV pre-exposure prophylaxis.)

A Phase III clinical trial showed that long-acting cabotegravir and rilpivirine works as well as daily pills for treatment-experienced people switching from a standard oral regimen with an undetectable viral load. Another study showed that Cabenuva also works well for those new to treatment who achieved viral suppression on a temporary oral regimen before switching to injections. However, these studies did not include people with unsuppressed virus or adherence challenges.

The Phase III LATITUDE trial (NCT03635788; ACTG A5359), sponsored by the National Institutes of Health (NIH), focused on people who face challenges using oral treatment. The study, ongoing at 31 sites in the United States, enrolled 434 people who either had poor virological response (persistent viral load above 200 despite oral ART for at least six months) or had been lost to clinical follow-up with ART nonadherence.

A majority of participants were men, the median age was 40 years and 20% were age 30 or younger. Nearly two thirds were Black, 27% were white and 17% were Latino. People with active drug or alcohol use or unstable housing were included; 14% had a history of injection drug use. About one in 10 had a high viral load (above 100,000) and the median CD4 count was quite low, at 270.

Participants first used a standard three-drug oral regimen for up to 24 weeks while receiving comprehensive adherence support and financial incentives to achieve viral suppression. Eligible participants who achieved a viral load below 200 were then randomly assigned to either continue on the same oral regimen or switch to cabotegravir and rilpivirine injections administered once monthly for a year.

As reported last month, the study was stopped early after an interim review found that Cabenuva "demonstrated superior efficacy in maintaining viral load suppression compared to daily oral therapy in individuals with a history of ART adherence challenges," according to a ViiV Healthcare news release.

At CROI, Aadia Rana, MD, of the University of Alabama at Birmingham, presented more detailed study results. A total of 294 eligible participants were randomized. More than 90% of people assigned to Cabenuva received their injections on time, while 3% had delayed injections and 3% missed injections.

At 52 weeks, 24% of people on Cabenuva and 39% of those on daily pills experienced regimen failure, meaning virological failure or treatment discontinuation. This primary endpoint narrowly missed the threshold for statistical significance, but secondary endpoints favored the injections.

Only 7% of those who received Cabenuva experienced virological failure compared with 25% who stayed on daily pills. Of these, two in each group had new resistance-associated mutations. What's more, 21% of Cabenuva recipients and 25% of standard-care recipients permanently stopped treatment. As seen in previous studies, cabotegravir and rilpivirine injections were safe and generally well tolerated. The most common adverse event was mild to moderate injection site reactions, such as pain, redness or nodules.

"Considering all endpoints together, [long-acting cabotegravir and rilpivirine] demonstrated superiority when compared to daily oral standard of care ART in people with HIV in the U.S. who face barriers to adherence and have a prior history of virologic non-response or loss to follow-up," the researchers concluded.

"Offering an effective alternative for people who have struggled with taking daily ART could provide life-changing freedom from the stress of unsuppressed HIV" Rana said in a news release. "If guidelines were to recommend broader use, it would be expected to have a large impact on rates of new HIV infections, as most are transmitted by persons with HIV who are aware of their diagnosis but are not virally suppressed," she told reporters at a CROI media briefing.

Injectables Without Viral Suppression

As noted, Cabenuva is approved only for people with viral suppression, so these study results do not apply to those who can't consistently use daily pills to get their HIV under control. Rana recommended that future clinical trials should assess this regimen in people with detectable HIV.

After Rana's presentation, Monica Gandhi, MD, MPH, medical director of the Ward 86 HIV clinic at Zuckerberg San Francisco General Hospital, pointed out that people with adherence challenges by definition often do not have viral suppression and need new options.

To that end, Gandhi's team conducted a pilot study of injectable cabotegravir and rilpivirine in the context of extensive support and services for people who are unable to maintain viral suppression due to adherence challenges.

This study included patients at Ward 86, a safety-net HIV clinic that serves mostly low-income people with public insurance, many of whom are dealing with substance use, mental health problems and unstable housing. This population differed from LATITUDE participants, reflecting San Francisco's HIV epidemic: Most were men, nearly half were age 50 or older and a majority were white or Latino. Nearly half had unstable housing and a majority used opioids, stimulants or both. Half had advanced immune suppression with a CD4 count below 200.

At the 2022 International AIDS Conference, the researchers reported initial results, showing that 12 of 15 people (80%) with detectable HIV at baseline achieved viral suppression, some for the first time. At CROI 2023, Gandhi reported results from a larger group of 133 people who started Cabenuva between June 2021 and November 2022. At baseline, 76 people already had an undetectable viral load on their existing oral regimen, and all maintained viral suppression after switching to injections. In a more groundbreaking finding, 55 of the 57 people (96%) who started

Cabenuva with a detectable viral load achieved viral suppression, comparable to response rates seen in pivotal clinical trials.

In an analysis presented at this year's CROI, the Ward 86 team assessed the durability of response in a retrospective cohort analysis of 59 people who started Cabenuva before December 2023, had a viral load of 50 or higher at baseline and had at least 56 weeks of follow-up time.

At 48 weeks, 81% met the primary endpoint of still being on Cabenuva (defined as no discontinuations or injections given more than 14 days late) with viral suppression. Seventeen had at least one injection more than seven days late, and eight had injections more than 14 days late. Five people stopped the injections and resumed oral ART. Overall, 93% maintained viral suppression on Cabenuva or another regimen. Two people experienced virological failure with resistance mutations despite on-time injections but regained viral suppression on alternative regimens (lenacapavir plus Biktarvy or cabotegravir plus lenacapavir). One had persistent low-level viral load even after adding lenacapavir. One stopped Cabenuva due to severe depression, and two were lost to follow-up.

While Ward 86 is well positioned to offer extensive support, this approach is not only feasible in cities like San Francisco. As reported last fall, a small case series showed that Cabenuva led to viral suppression in all 12 people without viral suppression who were treated at a Ryan White–funded HIV clinic at the University of Mississippi Medical Center.

New Guidelines and Future Directions

Based on these and other small studies, the International Antiviral Society-USA (IAS-USA) recently released updated treatment guidelines, published March 1 in JAMA.

"When supported by intensive follow-up and case management services," injectable cabotegravir and rilpivirine may be considered for people with detectable virus who are unable to take oral ART consistently, have a high risk of HIV disease progression and have HIV susceptible to both drugs "when no other treatment options are effective due to a patient's persistent inability to take oral ART," the new guidance states.

People with HIV who have advanced HIV disease and can't take oral ART (for whatever reason) are at high risk of OIs, cancers, and death.

Injectable CAB-RPV can be literally lifesaving--which is

why this change to the @IAS_USA guidelines is so important. https://t.co/1mml1VzT8u pic.twitter.com/qnlreFAtjs

— Paul Sax (@PaulSaxMD) March 1, 2024

One limitation of Cabenuva is that the regimen is less effective for people who have developed resistance to non-nucleoside reverse transcriptase inhibitor (NNRTIs) like rilpivirine. The 2024 World Health Organization drug resistance report shows that NNRTI resistance exceeds 10% in some countries, especially low- and middle-income countries.

In another poster at CROI, Gandhi and colleagues described a case series of people treated with long-acting cabotegravir plus lenacapavir.

As the sole HIV capsid inhibitor, lenacapavir remains effective against HIV that has developed resistance to other classes of antiretrovirals. It was approved in 2022 for heavily treatment-experienced people with multidrug-resistant virus. Lenacapavir is administered once every six months, but it has no equally long-acting partner, so it is usually used with daily pills. The cabotegravir and lenacapavir combination has not been studied in clinical trials, but the regimen holds promise, especially for countries where NNRTI resistance is more common.

Providers at Ward 86, the University of California San Diego's Owen Clinic, MetroHealth in Cleveland and the University of Pennsylvania HIV Clinic used cabotegravir (monthly or every other month) plus lenacapavir (every six months after an oral loading dose) to treat 34 people who had difficulty adhering to daily pills. About three quarters were men, the median age was 47 and more than half reported insecure housing, substance use or both.

The reasons for either adding lenacapavir to Cabenuva (68%) or using lenacapavir and cabotegravir without rilpivirine (32%) were documented or suspected NNRTI resistance (59%), integrase inhibitor resistance (15%), a high viral load when starting or switching to injectables (18%) and continued detectable virus on Cabenuva alone (12%). While just 16 had viral suppression at baseline, all but two (94%) achieved a viral load below 75 after starting lenacapavir. Again, treatment was safe and generally well tolerated, with injection site reactions being the most common side effect.

"Long-acting ART is expanding in high-income settings but is not accessible in low- and middle-income countries. We are in a situation akin to 2001, when entire conferences were full of data on the promises of oral ART without access to these lifesaving therapies worldwide," Gandhi told POZ. "We need alternative long-acting ART regimens, such as a combination of lenacapavir and cabotegravir, which will work against NNRTI-resistant virus."

“We wrote up this case series of individuals with mainly NNRTI-resistant virus on [lenacapavir and cabotegravir] to call for a larger trial of this combination in low- and middle-income countries,” she added. “The pharmaceutical companies who make each component have not worked together before, but advocacy seems to be working, and we will be initiating at least a small trial of this combination soon.”

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