Long-Acting Injectables Work Well for People Without Viral Suppression

Providing extra support can enable people with adherence challenges to achieve HIV suppression on Cabenuva.

March 19, 2025 By Liz Highleyman

Long-acting treatment with injectable cabotegravir and rilpivirine (Cabenuva) may be an option for people who are unable to maintain an undetectable viral load on oral antiretroviral treatment, especially if they received enhanced support, according to several studies presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2025) last week in San Francisco.

All modern antiretroviral therapy (ART) is effective and generally well tolerated, so treatment success often depends on 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. For some of these individuals, long-acting treatment may be a better option.

Cabenuva, the first complete regimen that doesn't require daily pills, is administered by injection once monthly or every other month. The Food and Drug Administration (FDA) approved Cabenuva in 2021 for people with viral suppression on a stable antiretroviral regimen, no history of treatment failure and no resistance to either drug. The Phase III ATLAS trial showed that Cabenuva works as well as daily pills for treatment-experienced people switching from a standard oral regimen with an undetectable viral load. The FLAIR trial found that it also works well for those new to treatment who achieved viral suppression on a temporary oral regimen before switching to injections.

Although people without viral suppression were not included in the pivotal trials that led to Cabenuva's approval, a growing body of real-world evidence shows that it can be a feasible option for this population as well.

Long-Acting Treatment in San Francisco

Monica Gandhi, MD, MPH, medical director of the Ward 86 HIV clinic at San Francisco General Hospital, and colleagues evaluated Cabenuva for people with a detectable viral load on oral treatment due to adherence challenges. This safety-net clinic serves mostly low-income people

with public insurance, many of whom are dealing with substance use, mental health problems and unstable housing or homelessness.

Gandhi's team first conducted a small demonstration study of Cabenuva in the context of extensive support and services. At the 2022 International AIDS Conference, they reported initial results showing that 12 of 15 people (80%) with detectable HIV at baseline achieved viral suppression, some for the first time. This set the stage for SPLASH, the Special Program on Long-Acting Antiretrovirals to Stop HIV. The program offers case management, phone or text reminders of upcoming injection visits, follow-up for those who miss appointments and street-based nursing services.

At CROI 2023, the researchers reported results from a larger group, showing that 55 of 57 people (96%) who started Cabenuva with a detectable viral load achieved viral suppression— comparable to the response rates seen in the pivotal Phase III trials. At CROI 2024, they presented follow-up results showing that 81% were still on Cabenuva with viral suppression at 48 weeks.

At this year's conference, Gandhi's team presented cumulative results for everyone with or without viral suppression (a viral load of at least 30 copies) who started Cabenuva between January 2021 and September 2024; the study findings were also published in JAMA.

Using electronic medical records, they evaluated outcomes for 370 participants, of whom 241 had viral suppression and 129 had a detectable viral load. Most (82%) were cisgender men, and 17% were transgender women or nonbinary. The median age was 45, and the study population was diverse: 41% white, 23% Black and 28% Latino. People with detectable HIV were more likely than those with viral suppression to report current or past substance use (61% versus 39%), have unstable housing (52% versus 40%) and have a CD4 T-cell count below 200, indicating advanced immune suppression (68% versus 44%).

Participants with a detectable viral load initially had to come in for injections visits each month, but the shots could be spaced out to every other month after they had viral suppression for three months. Participants received calls or texts to remind them of upcoming appointments, but they could also drop in for injections within a week of the scheduled date. Only five people, including three with detectable HIV, were lost to follow-up.

Among those who started long-acting ART with detectable HIV, the median time to achieve viral suppression was 32 days. At 24 weeks, 97% of people who started Cabenuva with a detectable viral load achieved viral suppression (200 copies or less), and all but one with undetectable HIV (99%) maintained viral suppression. At 48 weeks, they were still doing well, with 98% and 99%, respectively, having an undetectable viral load. Five people who achieved viral suppression on Cabenuva opted to switch to oral treatment for convenience or due to adverse events.

"In a program using long-acting ART for people with HIV, this study found that viral suppression with use of long-acting ART at 48 weeks was high and did not differ among individuals starting long-acting ART with or without viremia," the researchers concluded. "The low CD4+ cell counts

among those with viremia confirms this population was at high risk of continued disease progression."

In another San Francisco study, Kathleen O'Connor, of the SF Department of Public Health, and colleagues compared long-acting injectables versus oral treatment for people experiencing homelessness. According to the city's latest annual HIV epidemiology report, 31 homeless people were diagnosed with HIV in 2023, accounting for 23% of the 133 total new cases, and this population has among the lowest rates of viral suppression.

This retrospective analysis included 94 homeless people who received care at Maria X. Martinez Health Resource Center, a low-barrier public health clinic that also provides care at shelters and street medicine. A program started in 2023 offers enhanced monitoring and support for people unable to adhere to oral ART. A majority of participants had mental health disorders, nearly a third used opioids and more than 70% used stimulants.

Among those with at least two clinical encounters, 89 were on oral ART and 20 received long-acting ART during 2023 (15 switched from pills to injectables so were counted in both groups). Most received Cabenuva, but six received cabotegravir and lenacapavir (Sunlenca) with or without rilpivirine.

The study showed that everyone on long-acting injectables achieved and maintained viral suppression (below 200 copies), including 16 who started with a detectable viral load. In contrast, 61% of those on oral treatment achieved viral suppression at least once, and 46% maintained undetectable HIV at their latest follow-up visit. What's more, those in the long-acting ART group had more than twice as many clinical encounters (mean 27.6 versus 11.1 per person-year).

"These findings encourage increased public health investment in long-acting ART implementation, including within status-neutral safety net clinics designated for people experiencing homelessness," the researchers concluded.

Support Is Critical

The San Francisco findings support recent changes to the Department of Health and Human Services and International Antiviral Society-USA HIV treatment guidelines to include Cabenuva as a feasible option for people with detectable virus and adherence challenges, especially those at high risk for HIV disease progression.

Some experts, however, have expressed concern that starting Cabenuva without viral suppression might not work as well in settings that are not able to offer extensive support like Ward 86 or Maria X. Martinez Health Resource Center. Another study presented at CROI seems to bear this out.

Anthony Gerber, PharmD, of New York City Health and Hospital and colleagues evaluated outcomes among people who started long-acting injectable ART with and without viral suppression

(below 200 copies) in the country's largest municipal health system.

This analysis included 328 people who received at least one dose of Cabenuva between January 2021 and June 2024. Of these, 17 had a detectable viral load. Those with detectable HIV were more likely than those with viral suppression to be women (65% versus 34%), to have a CD4 count below 200 (63% versus 5%), to be on Medicaid (71% versus 47%) and to have detrimental social determinants of health (29% versus 15%), including financial insecurity and unstable housing.

In this study, people who started Cabenuva with a detectable viral load did not fare as well as those in San Francisco. The researchers found that 76% of those who started with detectable HIV had viral suppression (below 200 copies) on their most recent measurement, compared with 98% of those who started with an undetectable viral load. But surprisingly, using a viral load cutoff of 50 copies, the corresponding viral suppression rates were 71% and 66%, respectively.

"This study adds to the evidence that long-acting injectables are a vital option for patients with adherence challenges on oral ART," the researchers concluded. "Expanding FDA labeling to include patients with baseline viremia is essential to improve access, viral load suppression rates and overall health outcomes."

Other studies have looked at innovative use of long-acting injectables in the South, which bears the brunt of the U.S. epidemic. In 2023, researchers reported findings from a small case series showing that Cabenuva led to viral suppression in all 12 people with detectable HIV who were treated at a Ryan White-funded HIV clinic at the University of Mississippi Medical Center.

At CROI, Jonathan Colasanti, MD, MSPH, of Grady Health System's Ponce de Leon Center, and colleagues did a retrospective review of 361 people at a large Ryan White-funded clinic in Atlanta who received long-acting ART between April 2021 and August 2024 after struggling to achieve viral suppression on oral treatment. This program also provides intensive monitoring and appointment reminders.

Of these, 81 (22%) had detectable HIV when they started long-acting injectables. The median age was 38, and nine had lifelong HIV. More than 90% were Black. About a third were cisgender women, including four who started long-acting ART during pregnancy. The median CD4 count was only 186, and 44% had prior opportunistic infections, many of them recent due to unsuppressed virus. Detrimental social determinants of health were common. Most (56) started Cabenuva alone, 23 used Cabenuva plus lenacapavir and two used these meds plus ibalizumab (Trogarzo).

Of the 645 Cabenuva injections administered, 99% were on time. Two people were lost to follow-up before they received three Cabenuva injections. Of the remaining 79 people, 73 (92%) achieved viral suppression (below 50 copies) after one to two injections, resulting in the median CD4 count rising to 330. Of the six participants who did not achieve viral suppression, two had virological failure with drug resistance, two had persistent low-level viral load (below 200 copies) and two had long-standing viremia (1,000 to 3,000 copies) despite using Cabenuva and lenacapavir. Even with continued viremia, both experienced some immune recovery.

Based on these findings, the researchers concluded, “92% achieving viral suppression among people with HIV with a high burden of social determinants of health, late-stage HIV disease and prior challenges achieving viral suppression on oral therapies suggest a pathway toward Ending the HIV Epidemic goals.”

Treatment at Home

As these studies suggest, offering more support can help overcome barriers to treatment adherence and viral suppression.

Megan Dieterich, PA, of Whitman-Walker Health in Washington, DC, and colleagues evaluated an innovative support services program, including home administration of Cabenuva injections. Whitman-Walker started its Mobile Outreach Retention and Engagement (MORE) program in 2016 to support people with adherence challenges, as indicated by either a detectable viral load or no medical visits in six months. The program offers mobile care navigator support, transportation assistance and home medical visits; home administration of Cabenuva was added in 2023.

To date, 44 people have started Cabenuva through the MORE program, of whom 42 have been followed for more than four months. The median age was 44, 39% were women and 93% were Black. Over a quarter (27%) had detectable HIV at baseline. Two thirds of MORE participants opted to received Cabenuva injections at home; women and older people were more likely to do so. A matched standard care comparison group included 88 people who received Cabenuva according to its FDA indication (although 6% did have detectable HIV). Care navigators scheduled appointments and sent reminders for injections given at a clinic.

After four months, the MORE and comparison groups had similar rates of adherence (on-time injections; 88% versus 86%) and persistence (staying on Cabenuva; 92% versus 95%). 100% of MORE participants achieved or maintained viral suppression, as did 99% in the comparison group. That is, the MORE group fared equally well despite detectable HIV at baseline.

However, there were some differences. No one in the MORE group had late injections, compared to five in the comparison group. Two people in the MORE group missed injections and restarted Cabenuva and one missed a shot and started oral treatment. In the comparison group, three missed an injection and restarted Cabenuva, two missed a shot and started oral ART and two missed injections and were lost to follow-up. However, two MORE participants—but none in the comparison group—stopped Cabenuva and switched to oral ART due to injection site reactions.

“These findings suggest that the option for home injections can promote [Cabenuva] adherence in people with HIV with adherence challenges and boost provider confidence in prescribing injectable ART to populations most likely to benefit,” the researchers concluded. “Implementation strategies including at-home ART injections can help achieve national goals to end the HIV epidemic.”

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