Modern Integrase Inhibitor Regimens Work Well Over the Long Term

Once-daily Biktarvy, long-acting injectable Cabenuva and two-drug combos containing dolutegravir can keep HIV in check for years.

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Current integrase inhibitor–based antiretroviral treatment, including once-daily pills and long-acting injectables, are highly durable, controlling HIV for years, according to recent research. Even regimens that contain just two drugs can work well long term.

One study showed that Gilead Sciences' all-in-one pill Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) has kept HIV in check over five years of follow-up so far. ViiV Healthcare's newer long-acting injectable regimen Cabenuva (cabotegravir and rilpivirine) given every other month suppressed HIV for three years and counting. And two-drug oral regimens containing dolutegravir (including the Juluca and Dovato coformulations) held the virus at bay for more than six years in real-world use.

When multiclass antiretroviral therapy (ART) debuted in the mid-1990s, some people had trouble maintaining an undetectable viral load over the long term, and even occasional lapses in adherence could lead to drug resistance. What's more, early regimens were poorly tolerated and inconvenient, meaning that many people struggled to take them consistently. Thus, people with HIV were advised to plan ahead for their next regimen after the current one failed.

But antiretroviral treatment has come a long way over the past three decades, and this focus on regimen sequencing is no longer necessary for most people. In particular, modern integrase inhibitors are highly effective and well tolerated and have a high barrier to resistance.

Biktarvy for First-Line Treatment

Paul Sax, MD, of Brigham and Women's Hospital, and colleagues analyzed the long-term effectiveness of Biktarvy as an initial regimen in two pivotal Phase III trials. One study (NCT02607930) compared Biktarvy versus dolutegravir and abacavir/lamivudine (the drugs in the Triumeq combo pill), while the other (NCT02607956) tested Biktarvy against dolutegravir and tenofovir alafenamide/emtricitabine.

Participants were randomly assigned to receive Biktarvy or one of the comparator regimens. After 144 weeks of double-blind randomized follow-up, an open-label extension phase evaluated

Biktarvy through 240 weeks. Of the 634 study participants randomized to Biktarvy, 519 completed the blinded treatment phase, 506 opted for the 96-week extension and 444 stayed on this regimen for the full 240 weeks.

As reported recently in The Lancet, 98.6% maintained a viral load below 50 at 240 weeks in an "as treated" analysis that excluded people with missing virological data. In a second analysis that considered missing virological data as treatment failure, 67.2% maintained an undetectable viral load. What's more, the participants gained an average of 338 CD4 T cells. No treatment-emergent resistance to the drugs in Biktarvy was detected.

Only five participants (0.8%) stopped Biktarvy due to side effects. None did so due to kidney-related adverse events, and bone mineral density remained stable. (Tenofovir alafenamide is easier on the kidneys and bones than the older tenofovir disoproxil fumarate.) Total cholesterol rose by 21 milligrams per deciliter, and participants gained a median of about 13 pounds.

"Through five years of follow-up, [Biktarvy] maintained high rates of virologic suppression with no treatment-emergent resistance and rare drug discontinuations due to adverse events," the study authors concluded. "These results demonstrate the durability and safety of [Biktarvy] in people with HIV."

Cabenuva Every Other Month

In a second study, Edgar Overton, MD, of the University of Alabama at Birmingham and ViiV, and colleagues analyzed 152-week outcomes among people who received Cabenuva injections every other month.

The Food and Drug Administration initially approved Cabenuva as a once-monthly regimen. The Phase III ATLAS study (NCT02951052), which included more than 600 participants who started with an undetectable viral load on a standard daily oral regimen, showed that 93% of those who switched to once-monthly Cabenuva injections maintained a viral load below 50 at 48 weeks.

The follow-up ATLAS-2M trial (NCT03299049) compared Cabenuva taken monthly versus every other month. This study included 654 participants with an undetectable viral load who switched from a daily oral regimen and 391 people who rolled over from the monthly Cabenuva arm of the original ATLAS trial. They were randomized to receive Cabenua injections every four weeks or every eight weeks. At 48 weeks, 94% of participants in both groups maintained viral suppression, showing that the less frequent schedule was noninferior to monthly dosing.

The new results, published in Clinical Infectious Diseases, showed that Cabenuva remained highly effective at 152 weeks: 86% of participants in the monthly group and 87% in the every-other-month group maintained an undetectable viral load. Virological treatment failure was uncommon, but it occurred more often in the every-other-month group (0.4% versus 2.3%). Eight people developed resistance to rilpivirine, and 10 developed integrase inhibitor resistance. Treatment was generally well tolerated, with the most common side effect being transient mild to moderate injection site reactions.

These data “demonstrate virologic suppression durability” with Cabenuva every eight weeks or every four weeks for about three years and “confirm long-term efficacy, safety and tolerability of [Cabenuva] as a complete regimen to maintain HIV-1 virologic suppression,” the researchers concluded.

Dual Dolutegravir Regimens

Finally, Conor Bowman, MD, of Royal Free Hospital in London, and colleagues looked at outcomes among people treated with two-drug regimens containing dolutegravir in real-world clinical practice.

As described in the journal AIDS, 620 people with HIV were prescribed such regimens between January 2015 and October 2021—about 20% of the more than 3,000 people in the clinic database. Of these, 561 had complete data. About 80% were men, most were white and the median age was 54 years.

Nine people started treatment for the first time using a dual dolutegravir regimen, and all of them achieved viral suppression. The remaining 552 participants switched from their current, usually three-drug, oral regimen: 83.3% received dolutegravir plus lamivudine (the drugs in the Dovato combination pill), 13.4% received dolutegravir plus rilpivirine (the drugs in the Juluca combo pill) and 3.3% received dolutegravir plus emtricitabine. Most took separate pills, as the single-tablet regimen coformulations weren’t widely available until later in the study period.

Almost everyone who switched with an undetectable viral load maintained viral suppression, and the three dual regimens were similarly effective. A majority (62%) of those with a detectable viral load at baseline fell below 50 after the switch, but a couple experienced treatment failure.

Overall, 30 people (5.3%) experienced 41 viral “blips,” or one-off viral load readings above 50. This occurred more often among people who took separate pills than among those who used a single-tablet regimen. However, just six people (1.1%) experienced virological failure, defined as a confirmed viral load above 200 or persistent low-level viremia. One person, who experienced treatment failure with a high viral load, developed integrase inhibitor and reverse transcriptase resistance. Treatment was safe and generally well tolerated, but 12.5% stopped their two-drug regimen due to side effects.

“Overall, [a dolutegravir two-drug regimen] demonstrates high efficacy in [a] real-world setting,” the study authors concluded.

Taken together, these findings offer reassurance that people with HIV who start or switch to a modern antiretroviral therapy regimen containing an integrase inhibitor have excellent prospects for keeping the virus under control for years. Thanks to this effectiveness and durability, HIV-positive people on modern regimens who achieve viral suppression and maintain a high CD4 cell count can expect to live nearly as long as their HIV-negative peers.

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