Is Dolutegravir Alone Enough to Control HIV?

Only a small proportion of people who start treatment very early might be eligible for dolutegravir monotherapy.

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The potent integrase inhibitor dolutegravir kept HIV suppressed when used as monotherapy in a small study of people who started treatment at the earliest stages of infection, according to a recent report in Clinical Infectious Diseases. But experts caution that this approach is risky and could lead to the loss of viral control and the development of drug resistance if widely used.

Antiretroviral treatment has gotten much simpler over the past four decades, from handfuls of pills taken multiple times a day to single-tablet regimens that requite just one pill taken once daily. Dolutegravir has strong activity against HIV and a high barrier to resistance. Standard oral regimens have typically consisted of three drugs, but studies have shown that two-drug combinations containing dolutegravir—including the Dovato (dolutegravir/lamivudine) and Juluca (dolutegravir/rilpivirine) coformulations—are highly effective.

This raised the question of whether dolutegravir (sold alone as Tivicay) might work well enough on its own. Several studies have shown this is not the case for people who start treatment with established chronic HIV infection. But Emily West, MD, of University Hospital Zurich, and colleagues asked whether stand-alone dolutegravir maintenance therapy could provide sustained viral suppression in people who start treatment very early. Those who do so tend to have a smaller viral reservoir, less genetically diverse HIV and better preserved immune function, suggesting that they might be able to maintain control of the virus with a simpler regimen.

The EARLY-SIMPLIFIED trial (NCT02551523) enrolled 101 people in the Zurich Primary HIV Infection Study who started combination antiretroviral therapy within six months after primary infection and maintained an undetectable viral load for at least a year. Those with a prior history of treatment failure or existing integrase inhibitor resistance mutations were excluded. All but four were men, most were white and the median age was 42 years.

The participants were randomly assigned to stay on their combination regimen or switch to dolutegravir monotherapy. After 96 weeks, the randomized portion of the study ended, and participants could switch regimens as desired.

In 2019, the researchers reported that dolutegravir monotherapy was noninferior to combination therapy at 48 weeks, with 100% of participants in both groups maintaining an undetectable viral load (below 50 copies).

According to the new report, viral suppression was maintained with longer follow-up in both groups. At 96 weeks, everyone in both treatment arms still had an undetectable viral load. At the end of the study at week 192, no participants in either group had experienced virological failure. (One person who experienced virological failure in the monotherapy arm was excluded from the analysis after it was determined that he hadn't actually started treatment during primary infection.) While the earlier results suggested that the viral reservoir was decreasing faster in the monotherapy group, there was no significant difference at 192 weeks.

Dolutegravir monotherapy and continued combination therapy were both generally safe and well tolerated. Rates of adverse events did not differ much (22% versus 27%), despite the fact that the former group used more drugs. However, fewer people stopped treatment due to side effects in the monotherapy group (one versus five respectively).

"This trial suggests that early combination antiretroviral therapy initiation during primary HIV infection allows sustained virological suppression after switching to dolutegravir monotherapy," the study authors concluded.

Experts Urge Caution

These promising findings, however, do not apply to the vast majority of people with HIV who are diagnosed after the earliest stages of infection.

The French MONCAY trial, for example, included 158 people with chronic HIV who were on a stable regimen of dolutegravir/abacavir/lamivudine (the drugs in the Triumeq coformulation) with an undetectable viral load for at least a year. Here too, they were randomized to stay on that regimen or switch to dolutegravir monotherapy.

By week 24, two people in the dolutegravir monotherapy group experienced virological failure (defined as two consecutive viral load measurements above 50 within two weeks), though they did not develop integrase inhibitor resistance. At that point, viral suppression rates were 93.6% in the monotherapy arm versus 96.3% in the combination therapy arm.

With further follow-up, however, five additional cases of virological failure occurred in the monotherapy arm, two of which resulted in emerging integrase inhibitor resistance mutations. At week 48, the incidence of virological failure was 9.7% in the monotherapy arm compared with 0% in the combination arm. People with a lower nadir (lowest-ever) CD4 count were more likely to experience viral rebound. The trial's Data Safety Monitoring Board recommended that participants on monotherapy should resume standard combination therapy.

"Because the risk of virological failure with resistance increases over time, we recommend avoiding dolutegravir monotherapy as a maintenance strategy among people living with chronic HIV infection," the study authors concluded.

Likewise, a 2018 systematic review and meta-analysis found that 8.9% of dolutegravir monotherapy recipients experienced virological failure at 48 weeks, compared with just 0.7% of those on a two-drug regimen containing dolutegravir. Resistance mutations were observed in 3.6% of monotherapy recipients but none of those on dual therapy.

Based on these and other findings, "dolutegravir as maintenance monotherapy should no longer be considered a treatment option for patients outside or even inside the context of a clinical trial," Bart Rijnders, MD, PhD, and Casper Rokx, MD, PhD, of Erasmus Medical Center, wrote in a commentary accompanying the initial EARLY-SIMPLIFIED and MONCAY reports.

Indeed, the potential benefits of dolutegravir monotherapy are unlikely to exceed the risks.

Most people are diagnosed with HIV at later stages of infection and would not be candidates for this approach. In fact, less than a quarter of people screened for the EARLY-SIMPLIFIED trial were eligible. Determining primary infection and measuring viral reservoirs requires specialized testing that is often not available in routine care settings outside of clinical trials. However, given the shift toward rapid treatment immediately after diagnosis, the proportion of people with a smaller reservoir when they start therapy is likely to increase, the study authors suggested.

Three-drug and two-drug regimens are widely available as single-tablet coformulations, so monotherapy does not reduce pill burden. There is a good rationale for switching from a three-drug regimen to dolutegravir-based dual therapy, as commonly used third drugs, such as tenofovir disoproxil fumarate and abacavir, can cause problematic adverse effects. But the second drugs in Dovato and Juluca (lamivudine and rilpivirine, respectively) are well tolerated with minimal side effects.

The main advantage of dolutegravir monotherapy would appear to be cost savings: Tivicay costs roughly $500 less per month than Dovato and Juluca. But that savings comes with the possibility of losing the entire class of highly effective integrase inhibitors if resistance develops.

Commenting on Twitter, Boghuma Titanji, MD, PhD, of Emory School of Medicine, suggested taking the EARLY-SIMPLIFY results "with a large grain of salt." In addition to the small sample size of this study, "very early infection [is] hard to identify so few would be eligible," she wrote. Over time, they could ultimately experience viral breakthrough "with risk of losing a very potent [antiretroviral] drug class."

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