Switching to Dolutegravir and Lamivudine Works Well Despite Resistance Mutations

Using two instead of three or four drugs could potentially lead to cost savings in the billions.

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People who switched to dolutegravir plus lamivudine (the drugs in the Dovato combination pill) had a high likelihood of maintaining an undetectable viral load even if they had a history of prior treatment failure and a common lamivudine resistance mutation, according to study findings presented at the International AIDS Society Conference on HIV Science (#IAS2023). Another study found that people who experience temporary viral rebound while taking a first-line dolutegravir regimen can usually regain viral suppression after adherence counseling without changing their meds.

Switching from a standard regimen to dolutegravir/lamivudine would have a safety advantage if people stop taking a third drug such as tenofovir disoproxil fumarate or abacavir, according to presenter Gary Blick, MD, of Health Care Advocates International. Plus, the cost advantage of using two drugs instead of three or four could lead to savings “in the billions” for the Global Fund that provides treatment in low-income countries and for Medicaid in the United States, he added

Dolutegravir (sold alone as Tivicay) is a potent integrase inhibitor with strong activity against HIV and a high barrier to resistance. Dolutegravir/lamivudine is a recommended switch option for people with viral suppression who have no history of treatment failure and are not resistant to either drug, but many treatment-experienced people have a mutation known as M184V/I that confers resistance to lamivudine and the related drug emtricitabine.

The SOLAR-3D study asked whether people with a history of treatment failure who have the M184V/I mutation—or did so in the past—could nonetheless maintain viral suppression after switching to dolutegravir/lamivudine.

M184V/I does not make lamivudine completely ineffective, so dolutegravir would not be acting as monotherapy, Blick explained. In addition, the mutation tends to impair the fitness of HIV, reducing its ability to replicate. What’s more, the mutation may no longer persist in the viral reservoir of people with long-term viral suppression.

This prospective open-label trial enrolled 100 treatment-experienced adults on stable antiretroviral treatment with an undetectable viral load (below 50 copies) who switched to dolutegravir/lamivudine. Most (85%) were men, and the median age was 58 years. The median CD4 T-cell count at the time of the switch was just over 600, but about half had previously had a count below 200, the threshold for an AIDS diagnosis.

The participants had been diagnosed with HIV for a median of 25 years, had used a median of seven previous regimens and had maintained viral suppression for a median of about 12 years, but they had a history of prior virological treatment failure. They were using a variety of regimens at the time of the switch, most often dolutegravir/lamivudine/abacavir (the drugs in the Triumeq coformulation) or dolutegravir/rilpivirine (the drugs in Juluca). Half had M184V/I currently or in the past, while the other half had no evidence of ever having had the mutation. Those with M184V/I were older, had been living with HIV longer and had tried more regimens.

At the time of this 96-week analysis, the participants had been on dolutegravir/lamivudine dual therapy for a median of about 2.6 years. Next-generation sequencing of proviral DNA—reflecting the viral reservoir—showed that only 15 people (37% of those sequenced) who once had M184V/I still showed evidence of the mutation.

At 96 weeks, 84% of people who ever had M184V/I and 88% of those who never had the mutation had an undetectable viral load in an intent-to-treat analysis, which was not a significant difference. Excluding the 22 people who were missing viral load data for various reasons, the rates rose to 96% and 98%, respectively. Two people (4%) who ever had the mutation and one person (2%) who never did had viral blips above 50 copies. However, all regained viral suppression without changing their regimen, and there were no cases of confirmed virological failure or new drug resistance in either group. Treatment was safe and side effects were uncommon.

Through 96 weeks, SOLAR-3D demonstrated that “prior history [or] current presence of M184V/I doesn’t impact the efficacy of switching” to dolutegravir/lamivudine in virologically suppressed adults with multiple prior treatment failures, the researchers concluded.

Regaining Viral Suppression

Another study presented at IAS 2023 looked at the consequences of viral rebound among people taking different initial regimens. Andrew Hill, MD, of the University of Liverpool, and colleagues compared rates of virological failure and re-suppression in the ADVANCE trial, which evaluated first-line HIV treatment in South Africa.

World Health Organization guidelines recommend a switch to next-line antiretroviral treatment for people with a viral load of 1,000 copies or higher despite adherence counseling. Switching promptly is particularly important for people taking non-nucleoside reverse transcriptase inhibitors like efavirenz, as resistance to these drugs can develop rapidly. However, many people can regain viral suppression with no change to their regimen after they’re reminded of the importance of adherence and learn how to maintain it.

An intermittent viral load between 500 and 200 copies is generally considered a viral “blip.” In this study, the researchers defined virological failure as a viral load of 1,000 or higher after six months on treatment.

ADVANCE enrolled 1,053 people starting antiretrovirals for the first time. About 60% were women, almost all were Black and the median age was 32 years. They were randomly assigned to receive one of three regimens: dolutegravir plus tenofovir disoproxil fumarate/emtricitabine (the drugs in Truvada); dolutegravir plus tenofovir/alafenamide/emtricitabine (the drugs in Descovy); or efavirenz/tenofovir disoproxil fumarate/emtricitabine (the Atripla coformulation). Everyone with a viral load above 1,000 received enhanced adherence counselling.

The average time to initial viral suppression (50 copies or less) was significantly shorter with the two dolutegravir regimens versus the efavirenz regimen (four versus 12 weeks, respectively), but the rates of viral suppression and virological failure were statistically similar at 24 and 48 weeks.

Among people who had a viral load of 1,000 or higher after the first six months, 95% of those taking the dolutegravir-based regimens achieved an undetectable viral load by week 48 after adherence counseling, compared with just 66% of those taking efavirenz. What’s more, the time to regain viral suppression was significantly shorter with the dolutegravir regimens. No one whose viral load went above 1,000 in the dolutegravir groups developed resistance to integrase inhibitors, as seen in other first-line treatment studies.

In ADVANCE, although viral levels of 1,000 or higher were seen at similar rates across treatment arms, re-suppression after viral rebound was “significantly more likely” for people taking dolutegravir-containing regimens, according to the researchers.

“Long-term follow-up suggests most individuals on continued dolutegravir after viremia elevation can re-suppress with enhanced adherence counseling,” they concluded. “These results question the need for [a] switch to second-line protease inhibitors after virological failure on dolutegravir.”

Click here to read the SOLAR-3D abstract.

Click here to read the ADVANCE abstract.
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