Doravirine Combo Is Effective and Has Fewer Side Effects Than Atripla

The new single-tablet NNRTI regimen was less likely than Atripla to cause neurological symptoms.

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A new one-pill-once-daily combo containing doravirine, a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), is as effective as Atripla for first-time HIV treatment and causes fewer central nervous system and metabolic side effects, according to a report at the 9th International AIDS Society Conference on HIV Science (IAS 2017) that took place this week in Paris.

Modern first-line antiretroviral therapy is fortunately very safe and highly effective, but the availability of multiple potent and well-tolerated medications from different drug classes offers more opportunities to find the best regimen for each individual.

Kathleen Squires, MD, of Thomas Jefferson University in Philadelphia, presented findings from the DRIVE-AHEAD study, a Phase III trial comparing two single-tablet regimens for first-line HIV treatment:

- A new coformulation containing doravirine, lamivudine (3TC) and tenofovir disoproxil fumarate (TDF)
- Atripla, containing efavirenz (sold separately as Sustiva), emtricitabine and TDF.

Doravirine is an investigational NNRTI being developed by Merck that is active against HIV with common resistance mutations. It can be taken with or without food, and it is unlikely to interact with other medications.

DRIVE-AHEAD enrolled 728 people starting HIV treatment for the first time. About 85 percent were men, half were white and the median age was 31. Participants were randomly assigned to take the doravirine combination pill or Atripla for 96 weeks.

After 48 weeks on treatment, 84 percent of people taking the doravirine pill and 81 percent of those taking Atripla had undetectable viral load, defined as having HIV RNA below 50 copies per milliliter. Response rates were similar in the doravirine and Atripla groups regardless of whether

people started treatment with a high or a low viral load. These results show that the new doravirine coformulation is non-inferior, or equivalent, to Atripla.

Both treatments were generally safe and well tolerated, but there were some notable differences in side effects. In the doravirine group, half as many people reported drug-related adverse events (31 percent versus 63 percent), and fewer than half stopped treatment early because of adverse events (3 percent versus 7 percent, respectively).

The most common adverse events among people taking the doravirine pill were headaches, diarrhea and nose and throat inflammation. All occurred at similar rates among people taking Atripla.

But doravirine caused significantly fewer central nervous system side effects. For example, 9 percent of people taking the doravirine pill experienced dizziness, compared with 37 percent of those taking Atripla. Half as many people in the doravirine group reported sleep problems (12 percent versus 26 percent) or difficulty thinking or concentrating (4 percent versus 8 percent).

Blood fat levels also looked better in the doravirine group. Bad (LDL) cholesterol, total cholesterol and triglyceride levels decreased slightly after starting treatment with the doravirine pill, while increasing substantially after starting Atripla.

“Doravirine is a novel once-daily NNRTI for first-line treatment with consistent efficacy regardless of baseline viral load and favorable tolerability and safety profile in two Phase III clinical trials,” the study investigators concluded.

The other trial, called DRIVE-FORWARD, showed that people taking doravirine plus Truvada (TDF/emtricitabine) or Epzicom (abacavir/lamivudine) were as likely as those taking the boosted protease inhibitor darunavir (Prezista) to achieve an undetectable viral load. But again, people on doravirine were less likely to see rises in their cholesterol and triglyceride levels.

Some conference attendees wondered about the relevance of the DRIVE-AHEAD study because it compared the new doravirine pill to a regimen many consider old-fashioned.

Atripla is no longer widely recommended for first-time HIV treatment, in part because of its side effects. In fact, the latest U.S. government treatment guidelines don’t include any NNRTI-based regimens for first-time therapy. However, Atripla’s low cost and wide availability mean it is still often used in resource-limited countries.

Another concern is that the doravirine coformulation contains TDF instead of the new tenofovir alafenamide (TAF), which is safer for the kidneys and bones. This was done because a generic version of TDF is expected to become available soon (or it may not), while TAF is scheduled to remain under patent until 2022. Putting doravirine and TAF in the same pill would require Merck and Gilead to work together.