Poor Adherence, High Viral Loads Help Explain Rilpivirine Treatment Failures

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People who don't adhere to their antiretroviral (ARV) treatment regimen, or who start treatment with a high viral load, are more likely to experience virologic failure on a regimen containing rilpivirine (TMC278) than people on a regimen containing Sustiva (efavirenz). These data—along with information on the drug resistant HIV strains that most commonly developed in people who experienced rilpivirine treatment failure—were reported September 14 at the 50th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Boston.

Rilpivirine is an experimental non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by Tibotec for people who have never taken ARV drugs. Rilpivirine is nearing U.S. food and drug administration (FDA) approval, and the company is actively working on a fixed-dose formulation that combines the drug in a single pill with Gilead's Truvada (tenofovir plus emtricitabine).

Previous conference presentations of rilpivirine studies have revealed that the drug was more tolerable than Sustiva (efavirenz), the most widely used NNRTI in the United States. These studies also found, however, that people taking rilpivirine were a bit more likely to experience virologic failure than people taking Sustiva. Virologic failure was defined as: failing to get and keep virus levels under 50 copies on two consecutive viral load tests; having a 0.5 log increase in virus over the lowest ever measure; or having two consecutive viral loads over 50 copies after getting virus undetectable.

Explanations for Virologic Failure

To explore this pattern, Joseph Eron, MD, from the University of North Carolina in Chapel Hill, and his colleagues analyzed data from the ECHO and THRIVE studies, both of which compared rilpivirine with Sustiva in people new to ARV therapy, both paired with Truvada. As has been previously reported, rilpivirine was found to be comparable in efficacy to Sustiva, but with fewer side effects, particularly nervous system side effects.

In this analysis, Eron's team found that rilpivirine takers were more vulnerable to virologic failure if they started with a high viral load or had adherence challenges along the way. Fortunately, the majority of people in both studies began therapy with a viral load under 100,000, and most had good adherence. In this group, where adherence was high and virus levels low, there was no

difference in the rate of virologic failure between those on rilpivirine and Sustiva.

A difference began to emerge, however, in those with good adherence but high pre-treatment viral loads. While starting treatment with a high viral load made no difference in the rate of virologic failures in those taking Sustiva, it increased the likelihood of virologic failure by more than three times in those taking rilpivirine.

The difference between rilpivirine and Sustiva was more striking when adherence was taken into account, and this was true whether a person started treatment with a low or high viral load. In those with low viral loads, poor adherence led to twice as many virologic failures in those taking rilpivirine than in those taking Sustiva. In people with high viral loads, poor adherence made virologic failure three times more likely in those taking rilpivirine than in those taking Sustiva.

Patterns of Resistance

Another important issue is whether people had measurable drug resistance when they experience treatment failure. More resistance after treatment failure can decrease the list of available future treatment options.

Among those with virologic failure, about half as many people taking Sustiva had drug resistance to NNRTIs as those failing on rilpivirine. Among the NNRTI-resistant HIV strains analyzed, the most common among those failing Sustiva was the K103N mutation. This mutation, especially when found alone, doesn't appear to seriously jeopardize future treatment with the second-line NNRTI treatment Intelence (etravirine).

Among those failing on rilpivirine, however, the most common NNRTI mutation was the E138K, a relatively rare mutation. However, roughly 23 percent of those failing on rilpivirine had at least three NNRTI mutations. Both scenarios can reduce the likelihood that a future regimen that contains Intelence will work.

Mutations to nucleoside reverse transcriptase inhibitors (NRTIs), such as the drugs contained in Truvada, were about twice as common in those failing rilpivirine than in those failing Sustiva.
