NNRTI Etravirine Effective for Treatment-Experienced Patients

August 2, 2007 By Tim Horn

Results from two pivotal studies show that Tibotec's experimental non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (TMC-125), combined with their approved protease inhibitor (PI) Prezista (darunavir), is safe and effective for treatment-experienced HIV-positive patients. The 24-week study results were reported in two separate presentations at the fourth IAS Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, after being published in a July 7 edition of The Lancet.

The Phase III studies, called DUET-1 and DUET-2, are comparing etravirine (200 mg) to placebo, both combined with a background regimen in treatment-experienced patients with documented resistance to NNRTIs and PIs. For all patients, the background regimen includes Prezista (600 mg) plus Norvir (100 mg), along with a choice of nucleoside reverse transcriptase inhibitors (NRTIs). Patients were also given the option of using the approved entry inhibitor Fuzeon (enfuvirtide).

A total of 612 patients have been randomized and treated in DUET-1—304 in the etravirine/Prezista group and 308 in the placebo/Prezista group. In DUET-2, a total of 591 patients are enrolled and being treated—295 in the etravirine/Prezista group and 296 in the placebo/Prezista group.

At study entry, the average CD4 count in both studies was approximately 100 cells. Between 31 and 41 percent of those enrolled had viral loads above 100,000 at the start of the trial. Patients had used several PIs in the past and many—between 36 percent and 42 percent—had three or more detectable HIV mutations known to confer resistance to the current crop of NNRTIs. In addition, approximately 42 percent of patients in DUET-1 and 44 percent of patients in DUET-2 had three or more detectable HIV mutations known to confer resistance to Prezista.

Results from the DUET-1 study, reported by investigator Anthony Mills, MD, showed that significantly more patients (56 percent) in the etravirine/Prezista group had viral loads below 50 copies—undetectable—compared with those in the placebo/Prezista group (39 percent). In DUET-2, reviewed by Christine Katlama, MD, undetectable viral loads after 24 weeks were documented in 62 percent of those in the etravirine/Prezista group, compared to 44 percent of those in the placebo/Prezista group. In both studies, the differences between the two groups were statistically significant, meaning that they weren't likely due to chance.

Patients with high viral loads upon entering the study appeared much less likely to see their viral

loads drop below 50 copies in both studies, at least after 24 weeks of treatment. In DUET-1, for example, 68 percent of those in the etravirine/Prezista group with a baseline viral load below 100,000 had undetectable viral loads after six months, compared to 38 percent of etravirine/Prezista takers with pre-treatment viral loads above 100,000.

As for patients whose HIV was highly resistant to virtually all of the available antiretrovirals—meaning that they didn't have an active drug to use in their background regimens—47 percent of those in the etravirine/Prezista group in DUET-1 had undetectable viral loads after 24 weeks, compared to 9 percent of those in the placebo/Prezista group. Findings were similar in DUET-2.

Of note, when Fuzeon was used in the study by those trying it for the first time, virologic responses were similar between the etravirine/Prezista and placebo/Prezista groups in both studies. However, as the researchers only reported 24 weeks of follow-up data, it is likely too early to determine the value of adding etravirine to regimens containing Fuzeon (or another novel antiretroviral) in highly treatment-experienced patients.

As for side effects, the most frequent among etravirine/Prezista and placebo/Prezista recipients in DUET-1 were rash (20 percent vs. 10 percent respectively); nausea (14 percent vs. 12 percent); diarrhea (12 percent vs. 20 percent); headache (10 percent vs. 13 percent); nervous system disorders including headache, somnolence, dizziness, and memory impairment (15 percent vs. 20 percent); and psychiatric disorders including insomnia, anxiety, depression and nightmare (10 percent vs. 14 percent).

In DUET-2, the most common side effects were rash (14 percent vs. 9 percent respectively), diarrhea (18 percent vs. 20 percent), nausea (14 percent vs. 10 percent), injection site reaction (13 percent vs. 15 percent), headache (9 percent vs. 11 percent), fatigue (9 percent vs. 10 percent), nervous system disorders (15 percent vs. 17 percent) and psychiatric disorders (16 percent vs. 17 percent).

"The NNRTI class has been one of the cornerstones of antiretroviral therapy for more than a decade. However, NNRTI resistance limits the use of this class in treatment experienced patients," says Dr. Mills. "The results that we saw in DUET-1 and 2 in patients with documented NNRTI resistance are very exciting and suggest that in the future, we may have the ability to sequence NNRTIs in HIV treatment."
