Isentress Continues to Show Well Versus Sustiva as First-Line Treatment

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New 96-week data from a clinical trial of Isentress (raltegravir), Merck's integrase inhibitor approved for treatment-experienced patients by the U.S. Food and Drug Administration in October 2007, suggest that it has comparable long-term efficacy to Sustiva (efavirenz) in those starting treatment for the first time. The new data, which also indicate fewer side effects with Isentress, were reported yesterday, August 5, at the XVII International AIDS Conference in Mexico City by Martin Markowitz, MD, of the Aaron Diamond AIDS Research Center in New York.

Integrase inhibitors block a middle step in HIV's lifecycle. After HIV has entered a CD4 cell and its RNA has been reverse transcribed to viral DNA, it must then be integrated into the CD4 cell's DNA. The HIV DNA then hijacks the CD4 cell, turning it into a viral factory. Isentress blocks the viral DNA integration, hence its classification as an integrase inhibitor.

The new data comes from a two-part clinical trial of Isentress. The first part of the study, reported in November 2005, evaluated different doses of Isentress given as monotherapy (without other HIV drugs): 100 mg, 200 mg, 400 mg or 600 mg, all taken twice a day.

Dr. Markowitz's presentation focused on the research conducted in the second part of the study. It enrolled 198 HIV-positive people starting treatment for the first time—including 30 participants enrolled in part one of the study—to receive either Isentress at one of the six doses explored in part one of the study or Sustiva. After 48 weeks, all patients in the Isentress groups were switched to the twice-daily 400 mg dose. All patients in the study also received Viread (tenofovir) and Epivir (lamivudine).

Upon entering the study, average viral loads in the various treatment groups ranged from approximately 43,000 to 68,000.

Rates of undetectable viral loads—below 50 copies—were almost identical in both groups. After 96 weeks of therapy, 83 percent of patients in the Isentress group had viral loads below 50 copies; in the Sustiva group, 84 percent of patients had viral loads below 50. This difference between the two groups was too small to be considered statistically significant.

CD4 count increases were also similar among patients in both groups after 96 weeks or treatment. Among patients in the Isentress group, CD4 counts increased by 221 cells. In the Sustiva group,

CD4 counts increased by 232 cells. As with the viral load results, these differences were not statistically significant.

Dr. Markowitz reported that side effects were less frequent in the Isentress group, compared with the Sustiva group. Nausea (approximately 13 percent in both groups), dizziness (9 percent in the Isentress group vs. 29 percent in the Sustiva group), headache (9 percent vs. 24 percent, respectively), and diarrhea (7 percent vs. 11 percent, respectively) were the most frequently reported side effects. Neuropsychiatric adverse events—such as abnormal dreams, depression and suicidal thoughts—were less common in patients in the Isentress groups compared to those in the Sustiva group, occurring respectively in 16 percent and 32 percent of patients through week 48.

As for lipid levels, total cholesterol decreased my 1.1 mg/dL in the Isentress groups, compared to a 24.0 mg/dL increase in the Sustiva group. LDL “bad” cholesterol decreased by 5.8 mg/dL in the Isentress group, compared to an increase of 4.4 mg/dL in the Sustiva group. Differences between the Isentress and Sustiva groups with response to triglyceride and HDL cholesterol changes were not statistically significant.

An apparently unique adverse event seen in ten Isentress patients involved creatine phosphokinase elevations—a sign of muscle damage.

Isentress is currently approved by the FDA for treatment-experienced patients with drug-resistant HIV. Merck is planning to request for HIV-positive patients beginning therapy for the first time. And while Isentress currently requires dosing at 400 mg twice daily, Dr. Markowitz indicated that once-daily dosing—800 mg once daily—may be an option, but requires confirmation in follow-up studies.

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