# Isentress Has Long-Term HIV Efficacy and Safety, but Is Best Taken Twice Daily

March 3, 2011 By Tim Horn

The good news: Isentress (raltegravir)-based antiretroviral (ARV) therapy appears to work just as well as Sustiva (efavirenz)-inclusive regimens (such as Atripla), with fewer blood lipid problems, for at least three years in first-time HIV treatment takers. The not-so-good news: For best results using Isentress, twice-daily dosing is likely more effective than once-daily dosing in first-line drug regimens.

These are the conclusions of two studies presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI), held February 28 to March 2 in Boston.

Durable Efficacy: Long-Term Data From STARTMRK

The July 2009 approval of Isentress for people living with HIV starting therapy for the first time—it was initially approved for treatment-experienced patients in October 2007—was based on 48-week data from Merck's STARTMRK study comparing Isentress and Truvada (tenofovir plus emtricitabine) with Sustiva and Truvada. After one year of treatment in STARTMRK, 87 percent of those taking Isentress had an undetectable viral load after 48 weeks of treatment compared with 82 percent of those taking Sustiva. Isentress was therefore judged to have equivalent effectiveness to Sustiva.

As is typical with Phase III studies comparing two standard-of-care regimens, the STARTMRK researchers have opted to follow patients beyond the pre-determined 48- and 96-week trial period—for up to five years—to monitor the long-term safety and efficacy of Isentress. Three-year follow-up data were reported at CROI by Jürgen Rockstroh, MD, of the University of Bonn in Bonn-Venusberg, Germany.

STARTMRK enrolled 563 previously untreated HIV-positive individuals to receive either 400 milligrams (mg) Isentress twice daily or 600 mg Sustiva once daily, both in combination with Truvada. At study entry, the average viral load was about 100,000 copies and the average CD4 count was 218 cells.

After three years of treatment, according to the strictest data analysis performed by Rockstroh's

team, about 75 percent of Isentress-treated patients had undetectable viral loads (below 50 copies), compared with 68 percent of patients in the Sustiva group. Though Isentress appeared to do a better job of maintaining undetectable viral loads throughout the prolonged follow-up period, the study was not designed to determine the statistical superiority of one regimen over another.

Rates of virologic failure and resistance were also reported. In the Isentress group, about 17 percent experienced rebounds in viral load during the follow-up period, compared with 19 percent in the Sustiva group. In the Isentress group, one patient developed at least partial resistance to either Isentress or Sustiva, compared with four patients in the Sustiva group. Resistance to Isentress plus Truvada or to Sustiva plus Truvada was documented in three patients in both groups, and at least partial resistance to Truvada was documented in three Isentress-treated patients and two Sustiva-treated patients.

CD4 cell counts also increased in both study groups. Among those receiving Isentress, CD4s increased 332 cells over pre-treatment levels after three years of treatment. Among those receiving Sustiva, CD4s increased by 295 cells.
Metabolic parameters—such as blood lipids and body composition changes—were also reported by Rockstroh's group. Average levels of total cholesterol, "good" HDL cholesterol, "bad" LDL cholesterol and triglycerides were all more likely to increase in the Sustiva group compared with the Isentress group—all statistically significant differences, meaning unlikely to be due to chance.

Moderate to severe increases in total cholesterol, LDL cholesterol and triglycerides, to levels above those considered healthy, also appeared to be more common among those receiving Sustiva compared with Isentress. It was not clear, however, from the data presented that these differences were statistically significant.

A small number of patients (25 in the Isentress group and 32 in the Sustiva group) participated in studies evaluating changes in body composition, using dual energy x-ray absorptiometry (DEXA) scans conducted before starting treatment and after three years. Patients in both groups experienced increases in trunk fat, with a trend toward greater increases in the Isentress group (a 38 percent gain versus a 21 percent gain in the Sustiva group). The amount of fat in the extremities—such as the arms and legs—also increased in both groups, ranging from a 17 percent limb fat increase in the Isentress group and a 25 percent limb fat increase in the Sustiva group. Noting the rise in both trunk and limb fat, Rockstroh said the gains were "modest" and characteristic of the "return to health" phenomenon.

As for general tolerability of the two agents, Rockstroh noted that the overall incidence of drug-related side effects was lower for patients receiving Isentress compared with Sustiva (50 percent versus 80 percent), likely due to the central nervous system side effects of Sustiva.

In conclusion, Rockstroh reported, Isentress and Truvada "is associated with higher ARV efficacy and superior CD4 responses in treatment-naïve patients," compared with Sustiva and Truvada. In addition, he noted, "the long-term tolerability as well as metabolic profile appears favorable."

## Questionable Once-Daily Efficacy: Data From QDMRK

With Isentress's proven durability and safety—it is a preferred ARV for first-time treatment takers, according to guidelines maintained by the U.S. Department of Health and Human Services—there has also been interest in testing the drug for once-daily, instead of twice-daily, use. Results from Merck's QDMRK study, unfortunately, suggest this might not be the most effective option.

In the study, reported at CROI by Joseph Eron, MD, of the University of North Carolina, researchers randomized 770 people to take either 800 mg of Isentress once-daily or 400 mg of Isentress twice-daily, both in combination with Truvada.

People taking once-daily Isentress did well, with 83 percent having virus levels under 50 copies at week 48, but not as well as those taking twice-daily Isentress—89 percent of whom had undetectable virus after 48 weeks. While the results were close, the difference in response was large enough statistically that once-daily dosing failed to achieve the study goal, which was non-inferiority to twice-daily Isentress.

A deeper analysis showed that the greatest difference was in people who started treatment with viral loads over 100,000. Only 74 percent of those on once-daily Isentress with high pre-treatment viral loads had HIV levels under 50 copies at 48 weeks compared with 84 percent on twice-daily Isentress with high pre-treatment viral loads.

In patients with viral loads below 100,000, overall efficacy rates were comparable: 89 percent in the once-daily group had viral loads under 50 copies, compared with 92 percent of those in the twice-daily group. However, rates of virologic failure—viral load rebounds during the 48-week study—were still more common among once-daily Isentress users compared with twice-daily Isentress users: 18 failures versus 9 failures, respectively.

"Despite high virologic response rates in both [once-daily] and [twice-daily] arms, [once-daily Isentress] was inferior in virologic efficacy compared to [twice-daily Isentress]," Eron concluded.

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