Reyataz/Isentress Combo Spares Norvir and Nukes, But Is Integrase Resistance a Concern?

July 22, 2010 By Tim Horn

A regimen consisting of Reyataz (atazanavir) and Isentress (raltegravir)—used without low-dose Norvir (ritonavir) boosting or any nucleoside reverse transcriptase inhibitors (NRTIs)—is performing well in a clinical trial involving Norvir-boosted Reyataz plus Truvada (tenofovir plus emtricitabine) as a comparison, according to preliminary data reported Thursday, July 22, at the XVIII International AIDS Conference in Vienna. Of potential concern, however, are four cases of resistance to Isentress that have been documented thus far.

The pilot SPARTAN clinical trial, reported in Vienna by Michael Kozal, MD, of Yale University School of Medicine and his colleagues, was conducted in light of growing concerns about Norvir- and NRTI-associated toxicities. The study enrolled 94 treatment-naive people living with HIV: 63 were randomized to receive 300 milligrams (mg) Reyataz plus 400 mg Isentress, both taken twice a day, and 31 were randomized to standard treatment, which includes Norvir-boosted Reyataz (100/300 mg) plus Truvada once daily. Both study volunteers and the researchers knew which treatment regimen was being used.

Patients were, on average, 40 years old upon entering the study, and the vast majority of them were male (about 90 percent) and white (about 80 percent). Viral loads at study entry averaged 80,000 copies; roughly 50 percent had viral loads in excess of 100,000 copies before starting treatment.

About 10 percent of patients in each study group—six patients in the Reyataz/Isentress group and three patients in the standard treatment group—withdrew from the study by week 24. In the Reyataz/Isentress group, two withdrew consent, two dropped out because of jaundice, one because of an irregular heart rhythm and one due to lung cancer. In the standard treatment group, one was lost to follow-up, and two dropped out because of ECG abnormalities.

Six of the six subjects in the Reyataz/Isentress group had undetectable viral loads upon discontinuing treatment, Kozal noted.

In the strict intention-to-treat analysis, 74.6 percent of those in the Reyataz/Isentress group, compared with 63.3 percent of those in the standard treatment group, had undetectable viral

loads—below 50 copies—through week 24 of the study.

CD4s increased by 166 cells in the Reyataz/Isentress group, compared with 127 cells in the standard treatment group.

In a less-strict analysis, in which those who discontinued treatment were excluded, 81 percent of those in the Reyataz/Isentress group, compared with 70.4 percent of those in the standard treatment group, had viral loads below 50 copies after 24 weeks.

Failure to achieve or maintain a viral load below 50 copies by week 24 was documented in 11 Reyataz/Isentress patients (17 percent)—eight of whom had pre-treatment viral loads in excess of 250,000 copies—and eight standard treatment patients (26 percent)—four of whom had pre-treatment viral loads in excess of 250,000 copies.

Six patients (9.5 percent) receiving Reyataz/Isentress had viral loads in excess of 400 copies at week 24, compared with one patient (3 percent) in the standard treatment group.

Four of the six patients—6.3 percent of all Reyataz/Isentress-treated patients—with viral loads in excess of 400 copies at week 24 had evidence of Isentress resistance; none had evidence of Reyataz resistance. One of the remaining two patients had no known Isentress-resistance mutations; the sixth had an integrase gene that couldn't adequately be studied.

The one patient in the standard treatment group with a viral load in excess of 400 copies at week 24 had no evidence of resistance to either the protease inhibitors or NRTI being used.

Moderate-to-severe treatment-related adverse events were documented in 30.2 percent of those in the Reyataz/Isentress group and 33.3 percent of those in the standard treatment group. Moderate-to-severe increases in bilirubin—a known side effect of Reyataz treatment that can lead to yellowing of the eyes, skin and under the fingernails—was documented in 60.3 percent of those in the Reyataz/Isentress group, compared with 46.7 percent of those in the standard treatment group. Looking only at severe bilirubin increases, this occurred in 13 out of 63 (20.6 percent) of those in the Reyataz/Isentress group, compared with no severe bilirubin increases in the standard treatment group.

No significant differences between the two groups, with respect to lipid levels, through week 24 were reported. Some improvements were noted, however. For example, the total-to-"good" HDL cholesterol ratio was 4.4 in both groups at the start of the study, and it improved to 3.8 in the Reyataz/Isentress group and remained the same in the standard treatment group.

Before closing, Kozal provided a glimpse of some 48-week data, involving 70 patients who have been followed thus far. He said that 82.2 percent of those in the Reyataz/Isentress group, compared with 76 percent of those in the standard treatment groups, have maintained viral loads below 50 copies, with no additional subjects developing Isentress resistance since week 24 or patients developing Reyataz resistance in either group.

Kozal ended by noting that response rates to Reyataz/Isentress through 24 weeks of follow-up

were consistent with current standard of care. While no new safety issues emerged, rates of severe increases in bilirubin are clearly higher among those receiving Reyataz/Isentress. He also reiterated the development of Isentress resistance in four patients receiving Reyataz/Isentress, while taking comfort in the fact that no cases of Reyataz resistance were documented.

A similar study, exploring a nuke-sparing (but ritonavir-inclusive) first-line regimen consisting of Kaletra (lopinavir/ritonavir) plus Isentress, was reported in Vienna on Monday, July 19.

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