Some Gender and Racial Differences with Three Protease Inhibitors

August 5, 2008 By Tim Horn

Results using first-line treatment regimens containing three approved protease inhibitors may vary somewhat by race and gender, notably some side effects, according to a handful of studies reported August 5 at the XVII International AIDS Conference (IAC) in Mexico City. For the most part, however, treatment outcomes using these regimens are comparable in their safety and effectiveness among women and people of color.

As the HIV epidemic continues to diversify down racial and gender lines, both in the developing world and industrialized nations, health care providers and advocates have pressed manufacturers of ARVs to provide more complete information about possible racial and gender differences in treatment responses. Some manufacturers are responding to this need by conducting clinical trials that aim to recruit a sizeable percentage of women. Another approach is to re-review the results of completed studies to look for key racial and gender differences.

Five presentations at IAC involved racial and gender data from three completed protease inhibitor studies, all involving patients starting therapy for the first time. Two were from researchers associated with the Bristol-Myers Squibb–sponsored CASTLE study, comparing regimens containing twice-daily Kaletra (lopinavir/rtionavir) with regimens containing once-daily Norvir (ritonavir)-boosted Reyataz (atazanavir). Two presentations were from M05-730, an Abbott Laboratories study comparing once- and twice-daily Kaletra, also used in combination with other ARVs. The fifth was from Tibotec's ARTEMIS trial, a comparison of regimens containing Norvir-boosted Prezista (darunavir)—still considered experimental for patients new to HIV treatment—and Kaletra.

Norvir-Boosted Reyataz vs. Kaletra

In the CASTLE study, 78 percent of all patients in the Reyataz group, compared with 76 percent of all those in the Kaletra group, had viral loads below 50 copies after 48 weeks. Full 48-weeks results were recently published in The Lancet and were publicly presented most recently at the 15th Conference on Retroviruses and Opportunistic Infections (CROI) early this year in Boston.

Viral load responses to both regimens were consistently high a across all groups. Among black patients, rates were 71 percent in the Reyataz group and 78 percent in the Kaletra. Among Asian patients, the comparison was 83 percent and 90 percent, respectively. Seventy-seven percent of white patients taking Reyataz, compared with 73 percent of those taking Kaletra, had viral loads

below 50 after 48 weeks.

The magnitude of CD4 count increases was lowest among black patients for both regimens—an average CD4 gain of 142 cells among blacks taking Reyataz, compared with an average 190 CD4-cell gain in those taking Kaletra. Among white patients, gains were 226 and 204 cells, respectively. Among Asians, increases of 198 and 220 CD4 cells were reported.

As for responses among women—accounting for one-third of the overall study population—76 percent of those taking Norvir-boosted Reyataz for 48 weeks had viral loads below 50 copies, compared with 73 percent of those taking Kaletra. Among the men in the study, 79 percent of those taking Reyataz and 78 percent of those taking Kaletra had viral loads below 50 copies.

CD4 counts increased, on average, by 199 cells among the women receiving Norvir-boosted Reyataz, compared with a 221-cell gain among women taking Kaletra. Among the men, respective increases of 205 and 219 CD4 cells were reported.

With respect to side effects, the authors of both presentations noted that changes in total cholesterol levels and "bad" non-HDL cholesterol levels were consistently lower on Norvir-boosted Reyataz than Kaletra, regardless of race or gender.

The most notable racial trend in the data was an increase in triglycerides in the Kaletra group. There was a 100 percent increase in Asian patients and 60 percent increases in white and other racial groups. By contrast, triglyceride levels in the Reyataz group increased by 17 percent in whites, compared with 0 percent in blacks, Asians and other racial groups.

Moderate-to-severe diarrhea and nausea appeared more likely to occur among patients taking Kaletra compared with Reyataz, with the lowest rates seen in black and Asian patients. And juandice—yellowing of the skin, a documented side effect of Reyataz—occurred in 8 percent of whites and Asians and no black patients.

Rates of mild-to-moderate gastrointestinal side effects differed between women and men. Nausea, for example, occurred in 7 percent of women and 3 percent of men taking Reyataz. In the Kaletra group, 14 percent of women, compared with 5 percent of men, had mild-to-moderate nausea. Rates of other mild-to-moderate side effects differed by less than 5 percent between genders.

Once- vs. Twice-Daily Kaletra

Once- and twice-daily doses of Kaletra tablets have similar tolerability and comparable efficacy, according to overall 48-week results from M05-730 reported earlier this year at CROI.

About 500 of the study volunteers were white, 520 were men, 165 were people of color (73 percent of whom were black) and 144 were women. Pre-treatment viral loads were higher among whites and men. Pre-treatment CD4 counts were higher among whites compared with people of color, but similar among men and women.

After 48 weeks of treatment, study investigators reported at IAC, viral loads among all patients on Kaletra were below 50 copies in 77 percent of the whites, 75 percent of the non-whites, 78 percent of men and 72 percent of women. None of these differences was statistically significant, meaning they could have been due to chance.

CD4 cells increased with similar magnitude among white and non-white patients. The average increase among whites was 194 cells after 48 weeks, compared with 185 among people of color.

CD4 increases were also similar between male and female participants. The only statistically significant difference was among patients starting treatment with fewer than 50 CD4 cells—after 48 weeks, CD4s increased by 237 among women, compared with 167 among men.

The most common moderate-top-severe side effects were diarrhea, nausea and vomiting. Among white patients taking either once- or twice-daily Kaletra, moderate-to-severe diarrhea occurred in 18 percent. Among non-white patients taking either once- or twice-daily Kaletra, moderate-to-severe diarrhea occurred in roughly 10 percent. Gastrointestinal side effects occurred with similar frequency in men and women.

Moderately severe increases in triglyceride levels were noted in 1 percent of women and 6 percent of men. However, the study authors noted that men in the study tended to start with higher triglycerides than female patients.

No differences in moderate-to-severe laboratory abnormalities were reported in whites compared with non-whites.

Norvir-Boosted Prezista vs. Kaletra

Although Prezista may be approved only for treatment-experienced patients, data from the ARTEMIS study suggest that it may also have a lot to offer those starting treatment for the first time. Combined with a low-dose Norvir booster, it is comparable to Kaletra, according to data presented in September at 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Chicago.

At IAC, researchers presented an analysis evaluating safety and efficacy results according to race and gender. Of the people included in the analysis, 137 were white, 80 were black, 77 were Hispanic and 44 were Asian; 239 were male and 104 were female.

Rates of men and women with viral loads below 50 copies after 48 weeks were identical—84 percent in both groups. A whopping 100 percent of Asians had viral loads below 50 copies after 48 weeks, compared with 83 percent of blacks, 80 percent of whites and 82 percent of Hispanics. The authors note, however, that the actual number of Asians enrolled in the study was too small to draw any strong statistical conclusions.

Researchers did not report on changes in CD4 cells.

With the exception of diarrhea—observed more frequently in men than in women—and vomiting—observed more frequently in women than men—rates of side effects were similar between the two sexes.

As for racial differences and rates of side effects, there was a lower rate of nausea and higher rate of back pain in black patients (9 percent vs. 14 to 20 percent of whites, Asians and Hispanics; and 13 percent vs. 0 to 8 percent, respectively). There was also a lower incidence of headache, diarrhea and abdominal pain (2 percent vs. 17 to 32 percent of whites, blacks and Hispanics) but a higher rate of upper respiratory tract infections in Asian patients (27 percent vs. 9 to 19 percent). A higher rate of rash was documented in Hispanic patients (14 percent vs. 5 to 7 percent of whites, blacks and Asians). Finally, there was a lower rate of urinary tract infections in Asians and whites (0 to 1 percent vs. 8 to 14 percent of blacks and Hispanics). The authors stressed, however, that these differences were not considered to be “clinically relevant.”

The only notably difference in laboratory abnormalities was a higher rate of amylase increase—a marker of possible pancreatitis, an inflation of the pancreas—in black patients.

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