### Intracranial Hemorrhage Risk Prompt Changes to Aptivus Label

**By Fran Lowry**

**Orlando Bureau**

**Toronto** — Adding a fourth drug to a standard three-drug regimen in the initial treatment of HIV-infected subjects has no advantage in terms of tolerability or safety, according to a study presented at the 16th International AIDS Conference.

The high rates of virologic suppression achieved in this study support current guidelines that recommend two nucleosides plus efavirenz among preferred regimens for the initial treatment of HIV-1 infection. Adding abacavir as a fourth drug to the standard initial three-drug regimen did not change toxicity or adherence but provided no additional benefit, said Dr. Roy M. Gulick of Weill Cornell Medical College, New York.

The standard three-drug regimen is effective for most individuals with HIV, but some researchers have hypothesized that if three is good, four must be better. Dr. Gulick said at a press briefing, “To test this theory, the AIDS Clinical Trials Group (ACTG) A5095 study looked at 765 treatment-naive subjects in a double-blind, placebo-controlled study conducted between March 2001 and March 2005. The patients were randomized to a three-drug regimen consisting of zidovudine/lamivudine plus efavirenz (382 patients) or to a four-drug regimen consisting of zidovudine/lamivudine/abacavir plus efavirenz (383). The primary objectives of the study were to determine the safety and tolerability of the two regimens, to show a noninferior rate of virologic failure with the four-drug regimen compared to the three-drug regimen, and to compare time to virologic failure between the two treatments. Virologic failure was defined as two consecutive HIV RNA measurements that were at least 200 copies/ml at week 16 or later.

Overall, the results of the two regimens were virtually identical, Dr. Gulick said. With a median of 3 years of follow-up, virologic failure occurred in 99 (26%) of subjects on the three-drug regimen and 94 (25%) of subjects on the four-drug regimen. Similarly, time to first virologic failure did not differ significantly between the two groups. Virologic load was also similar with the two regimens at 3 years, as were the CD4 cell counts and incidence of adverse events.

The study participants did well, with more than 80% reducing their HIV RNA levels to less than 50 copies/ml at 3 years, he noted. “Our study affirms that the three-drug regimen we use to treat HIV infection today is very effective for most people, and adding a fourth drug is of no benefit in terms of decreasing viral load levels or increasing T cells,” Dr. Gulick added in an interview.

### Efavirenz-Based Treatment Better at Reducing Viral Load

**By Fran Lowry**

**Orlando Bureau**

**Toronto** — A large, randomized comparison of three standard regimens for initial treatment of HIV has shown that efavirenz plus two nucleosides was significantly better at reducing HIV viral load, investigators said at the 16th International AIDS Conference.

The regimens for first-line therapy of HIV that are currently recommended by the Department of Health and Human Services are the protease inhibitor lopinavir and the nonnucleoside reverse transcriptase inhibitor efavirenz, each given with two nucleoside reverse transcriptase inhibitors.

However, these regimens have not been compared in adequately powered, randomized clinical trials. Nor has the nucleoside-sparing regimen of efavirenz plus lopinavir plus abacavir, said Dr. Sharon A. Riddler, of the University of Pittsburgh.

Dr. Riddler and her coinvestigators of the open-label, prospective AIDS Clinical Trials Group (ACTG) 5142 study compared these three regimens in 753 naive subjects with HIV RNA greater than 2,000 copies/ml and any CD4 cell count. Participants were randomized equally to one of three arms: lopinavir soft gel capsules plus two nucleosides, efavirenz plus two nucleosides, and lopinavir soft gel capsules plus efavirenz. With a median follow-up of 112 weeks, the time to virologic failure was significantly shorter in the lopinavir plus two nucleosides arm, compared with the efavirenz plus two nucleosides arm. At week 96, the proportion of subjects without virologic failure was 76% in the efavirenz plus two nucleosides arm, 74% for lopinavir plus efavirenz, and 67% for lopinavir plus two nucleosides.

“Our findings suggest that the efavirenz plus two nucleosides was the best of the three approaches as initial therapy, even in patients with relative low CD4 cell counts,” she said.

“Before this study, a large randomized trial had shown that the nucleoside-sparing regimen was not inferior to the efavirenz plus two nucleosides regimen,” Dr. Riddler said. “In this study, we showed that the nucleoside-sparing regimen was noninferior to the efavirenz plus two nucleosides regimen.”

Older HIV Patients More Likely To Comply With Treatment

**By Fran Lowry**

**Orlando Bureau**

**Toronto** — With age comes enhanced adherence to HIV therapy, according to a study presented at the 16th International AIDS Conference.

Michael J. Silverberg, Ph.D., of Kaiser Permanente’s Division of Research, Oakland, Calif., and his associates took a prospective look at 5,000 patients in their region from 1995 to 2004. Of those, 1,000 were aged at least 50 years. All were in the Kaiser Permanente Northern California health plan for the 6 months prior to antiretroviral therapy. They found that subjects over age 50 were more adherent to highly active antiretroviral therapy (HAART)—a cocktail of a protease inhibitor plus two reverse transcriptase inhibitors—than were younger patients.

As a result, they were 15% more likely to reach undetectable levels of HIV infection and had higher CD4 counts.

**Dr. Silverberg**

Older patients were 15% more likely to reach undetectable levels of HIV infection and had higher CD4 counts. Laboratory abnormalities frequently seen after initiation of HAART in older individuals included hyperglycemia, abnormal lipids, hypertension, or alcohol abuse—were not seen in older patients. These good results were entirely due to their excellent adherence, he added.

Patients older than 30 years were more likely to achieve HIV RNA levels of less than 500 copies/ml, and, like patients aged 40-49 years, they had a blunted immune response in the first year of therapy. That response was compensatory, for, however, faster subsequent increases in CD4 cell counts were seen. Although viral loads were lower, CD4 cell counts were higher.

**Dr. Silverberg**

Older patients were more likely to have more comorbidities such as metabolic syndrome, abnormal blood lipids, and heart disease, which was linked to a higher viral year incidence of laboratory abnormalities. In addition, HAART was associated with reduced tolerability of the drugs. Laboratory abnormalities frequently seen after initiation of HAART in older individuals included hyperglycemia, abnormal lipids, abnormal blood lipids, and heart disease, which was linked to a higher viral year incidence of laboratory abnormalities. In addition, HAART was associated with reduced tolerability of the drugs.

“Because of these abnormalities, we feel that older patients need special close monitoring, especially at the beginning of antiretroviral therapy,” Dr. Silverberg said. “However, they do quite well. I guess with age, people become more disciplined with their treatment,” he added.