Four Drugs No Better Than Three for Initial HIV Tx

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, according to research 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.

'Adding a fourth drug is of no benefit in terms of decreasing viral load levels or increasing T cells.'

DR. GULICK

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, and to compare the 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 all are safe and effective, but a regimen of 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, 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% for those in the efavirenz plus two nucleosides arm, 74% for lopinavir plus efavirenz, and 67% for lopinavir plus two nucleosides, Dr. Riddler reported.

"Our findings suggest that the efavirenz plus two nucleosides was the best of the three approaches as initial therapy, even in patients with relatively advanced HIV disease," she said.

"The main message from this study is that it is an incremental step toward understanding the most useful regimens to be used for initial therapy in HIV-infected individuals," Dr. Riddler said in an interview. "All of the three regimens were effective, with significant increases in CD4 cell counts and the vast majority of individuals having undetectable viral loads, regardless of which regimen was initiated."

ACTG 5142 "is the first study to look at these three standard-of-care regimens in naive individuals randomized upfront, and the data are important for how we actually tease out a lopinavir-based regimen compared to an efavirenz-based regimen," said Dr. Scott M. Hammer, professor of medicine at Columbia University, New York, and an ACTG investigator. ■

Intracranial Hemorrhage Risk Prompts Changes to Aptivus Label

Reports of fatal and nonfatal intracranial hemorrhage among HIV-1 infected patients taking Aptivus (tipranavir) in combination antiretroviral therapy have prompted the manufacturer to issue new safety information.

Boehringer Ingelheim Pharmaceuticals Inc. has identified 14 reports of intracranial hemorrhage, including 8 fatalities, in 6,840 HIV-1 infected individuals receiving Aptivus capsules coadministered with ritonavir (Norvir) (500 mg/200 mg twice daily).

Many of these patients who developed intracranial hemorrhage had other medical conditions—CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, or alcohol abuse—or were receiving concomitant medications, including anticoagulants and antiplatelet agents, that may have caused or contributed to these events.

Several sections of the label have been changed to reflect concerns about using the drug in patients at increased risk of bleeding.

No pattern of abnormal coagulation parameters has been identified in patients receiving Aptivus in general or preceding development of intracranial hemorrhage. For this reason, routine measurement of coagulation parameters is not currently indicated for the management of patients taking the drug.

Aptivus/ritonavir therapy should be used cautiously in patients who may be at risk for increased bleeding from trauma, surgery, or medical conditions, or who are taking other drugs known to increase the risk of bleeding. Of note, patients with advanced HIV disease/AIDS have been observed to have an increased risk of intracranial hemorrhage. Investigations are ongoing to determine the role of Aptivus in the development of intracranial hemorrhage.

For more information or to report adverse reactions, contact Boehringer Ingelheim Pharmaceuticals by calling 800-542-6257 (option 4). Adverse reactions can also be reported to the Food and Drug Administration's MedWatch program by calling 800-332-1088.

—Kerri Wachter

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 about 5,000 patients in their registry 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.

Older patients were 15% more likely to reach undetectable levels of HIV infection and had higher CD4 counts.

DR. SILVERBERG

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 after 3 years of HAART than did their younger counterparts, Dr. Silverberg said. These good results were entirely due to their excellent adherence, he added.

Patients older than 50 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 compensated for, however, by faster subsequent increases in CD4 cell counts compared with those of 18 to 39-year-old patients, Dr. Silverberg reported.

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 first-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 bilirubin, neutrophil, ALT and AST levels, and elevated creatinine, Dr. Silverberg said.

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