Interrupted HIV Treatment Has Persistent Risks

BY DIANA MAHONEY
New England Bureau

BOSTON — The increased risk of disease progression, AIDS, and death associated with structured treatment interruptions in HIV-positive patients is diminished but not fully reversed when continuous therapy is resumed, according to the final results of the largest HIV therapy trial to date.

A treatment strategy that includes interruptions in antiretroviral therapy (ART) guided by patients' CD4 cell counts was deemed detrimental in 2006 by investigators in the Strategies for Management of Antiretroviral Therapies (SMART) trial. The trial was halted and all patients were encouraged to resume therapy, based on interim data showing that patients who used ART only when their CD4 cell counts fell below a threshold had higher rates of AIDS-related opportunistic illnesses, serious nonopportunistic events, and all-cause mortality than patients who stayed on continuous therapy.

"Following the recommendation to reinitiate antiretroviral therapy for patients in the treatment interruption group, the risk of opportunistic disease or death was significantly reduced, but the [risk reduction] was less than complete," Dr. Wafaa El-Sadr of New York's Harlem Hospital Center reported at the 15th Conference on Retroviruses and Opportunistic Infections. Patients who resumed treatment and were on continuous therapy for at least 85% of the 18 months following study modification reaped the most benefit from treatment reinitiation, she said.

The SMART trial enrolled 5,472 HIV-positive adults with CD4 cell counts of at least 350 cells/mm^3 at study inception. Patients were randomized to either the drug conservation arm, in which they used antiretroviral therapy only when their CD4 cell count fell below 350 cells/mm^3, or the viral suppression arm, in which they remained on antiretroviral therapy throughout the study.

Treatment interruption was linked to higher rates of AIDS-related opportunistic illnesses, serious nonopportunistic events, and all-cause mortality.

Before the study was modified, patients in the conservation arm had spent 36% of the trial on treatment, with a median of three treatment interruptions over an 18-month period, while patients in the viral suppression arm spent 94% of the time on treatment, Dr. El-Sadr noted.

At the time of modification, 35% of the conservation patients and 82% of the suppression patients had an undetectable viral load (less than 400 copies/mL), and the respective median CD4 counts were 425 and 625 cells/mm^3, she said.

After the study modification, patients who had been in the conservation group spent 71% of the follow-up time on treatment, compared with 91% in the suppression group, Dr. El-Sadr said. At the end of the study, 83% and 95% of the conservation and suppression patients, respectively, were on treatment, she said.

With respect to CD4 cells, the percentage of time the conservation group spent with counts lower than 350 cells/mm^3 fell from 31% before the study was modified to 23% at the end of follow-up. The percentage of time the suppression group spent with CD4 cell counts lower than 350 cells/mm^3 fell from 8% to 7%, Dr. El-Sadr reported.

Before the study was altered, the outcome rates of opportunistic disease or death per 100 person-years were 3.4 in the conservation arm and 1.4 in the suppression arm. The respective rates per 100 person-years for death due to any cause and a composite outcome of serious cardiovascular, kidney, and liver events were 1.5 and 1.8 in the conservation arm, compared with 0.8 and 1.1 in the suppression group.

At final follow-up, the rates for all three outcomes declined significantly in the conservation arm and remained stable in the suppression arm. For example, the rate per 100 person-years of opportunistic disease or death among those who reinitiated treatment was 2.1, compared with 1.4 for the suppression group. The rates per 100 person-years of death from any cause and of composite serious events were 1.3 and 1.1 in the conservation group, vs. 0.9 and 0.9 in the suppression group, she said.

Patients who had developed a nonfatal opportunistic disease or cardiovascular disease and those who had a renal or liver event prior to study modification had a nearly sixfold increased risk of death after the study was altered, she reported.

The "less than full" risk reversal following treatment reinitiation in the drug conservation group could be a consequence of a lower average CD4 cell count and the increased number of patients with detectable viral load, which was likely associated with a failure to resume continuous therapy as recommended, Dr. El-Sadr said. The findings, she said, support the recommendation against antiretroviral therapy interruption based on CD4 cell threshold. ■

HIV Patients Have Higher Osteoporosis Risk

BY NANCY WALSH
New York Bureau

BOSTON — An increased risk for osteoporosis or osteopenia is among the age-related complications faced by patients surviving long term with HIV disease.

Cross-sectional studies have shown that patients with HIV have a greater prevalence of reduced bone mineral density, compared with healthy controls, but longitudinal data that would demonstrate the significance of this increased risk are lacking, said Dr. William G. Powderly of University College Dublin.

To meet this need for data, the Centers for Disease Control and Prevention is prospectively following a cohort of more than 500 HIV-infected patients in the Study to Understand the Natural History of HIV and AIDS (SUN), Dr. Powderly said at the 15th Conference on Retroviruses and Opportunistic Infections.

On enrollment in SUN, patients had baseline bone densitometry and body composition measurements, clinical data, and fasting laboratory data collected, and were matched for age, race, sex, and body mass index with controls from the National Health and Nutrition Examination Study III.

Among the SUN patients (mean age 41 years), 52% had osteopenia and 10% had frank osteoporosis, Dr. Powderly said. A total of 78% were men, 25% were black, and almost 80% were receiving antiretroviral therapy.

Analysis revealed that factors associated with an increased risk of low bone mineral density included age over 45 years (odds ratio 2.35) and CD4 count below 300 cells/mm^3 (OR 2.10), Dr. Powderly said.

Duration of HIV infection longer than 98 months also was associated with an increased risk (OR 1.56).

Determining whether bone mineral loss will continue over time and translate into increased risk for fractures is a "critically important" area of HIV research, Dr. Powderly said at the meeting, which was sponsored by the Foundation for Retrovirology and Human Health and the CDC.

Aside from risk factors also present in the general population such as smoking, alcohol use, low body mass index, and lack of physical activity, the aging HIV patient also might have renal dysfunction and inadequate nutrition, which can further contribute to bone loss.

HIV disease itself might alter the processes involved in bone mineralization and turnover, according to Dr. Powderly. In a study he and his colleagues performed, human osteoblast and mesenchymal stem cell lines were treated in vitro with several HIV proteins. Exposure to these proteins reduced calcium deposition, alkaline phosphatase activity, and mRNA levels of osteogenic transcription factors in osteoblasts, and the ability of stem cells to develop into osteoblasts was modulated (AIDS Res. Hum. Retroviruses 2007;23:1521-30).

There is also some evidence implicating potent antiretroviral medications in bone loss. In a meta-analysis of 20 studies that included 884 patients, 67% had reduced bone mineral density and 15% had osteoporosis. Those receiving antiretroviral therapy had a 2.5-fold increased risk of having reduced bone mineral density, compared with those who were treatment naive (AIDS 2006;20:2165-74).

The dynamic process of bone mineralization is another factor. "We reach the peak of bone mineralization at around 30 years, and then both men and women lose bone at a rate of approximately 0.5%-1% per year," he said. "But we have no data on peak bone mineralization in HIV patients. It's quite possible that the high rates of osteoporosis and osteopenia we are seeing in these patients is not a result of accelerated bone mineral loss but because for some reason they never reached the same peak mineralization as healthy individuals," Dr. Powderly said.

"Sorting out risk factors, the HIV effects, and the treatment effects in such a multifactorial situation is not going to be easy," he noted.

Until the relative contributions to bone loss of the various factors can be clarified, the routine care of older patients with HIV should include monitoring of markers of bone turnover, he said. ■

Gene Test Identifies HIV Drug Reaction

Patients with HIV who do not carry the HLA-B*5701 allele are at very low risk for a hypersensitivity reaction to the antiviral drug abacavir, researchers reported.

For that reason, a pharmacogenetic test—screening for the HLA-B*5701 variant—now can be used to prevent a specific toxic effect of a drug, according to Dr. Simon Mallal of Royal Perth (Australia) Hospital and his associates.

The investigators conducted the Prospective Randomised Evaluation of DNA Screening in a Clinical Trial (PREDICT-1) in 1,956 adults with HIV who were treated at 265 medical centers in 19 countries. A total of 847 patients who served as the control group began usual treatment with abacavir without HLA-B*5701 screening. Participants' mean age was 42 years, with a range of 18-76 years.

Another 803 patients first underwent HLA-B*5701 screening, and those who were found to carry the variant were excluded from abacavir therapy. Their mean age was 42 years, with a range of 18-77 years. The remaining HLA-B*5701-negative patients received abacavir. Both groups were observed over 6 weeks for hypersensitivity reactions.

No hypersensitivity reactions developed in patients who were not carriers of HLA-B*5701. In the control group, approximately half of the patients later found to be HLA-B*5701 carriers had a hypersensitivity reaction to the drug.

The HLA-B*5701 allele had a negative predictive value of 100% and a positive predictive value of 48%, Dr. Mallal and his associates said (N. Engl. J. Med. 2008; 358:568-79).

"HLA-B*5701 carriage clearly demarcated a high-risk group of patients, accounting for approximately 6% of the population, from the remaining 94% who were at low risk for a hypersensitivity reaction to abacavir," they said.

The study was supported by GlaxoSmithKline, and several of the investigators disclosed relationships with the company. Dr. Mallal disclosed that he is the sole shareholder for a company that has a patent pending for HLA-B*5701 testing.

—Mary Ann Moon