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 reinitiated, 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 Therapy (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-defining illnesses, serious opportunistic 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 3,472 HIV-positive patients with CD4 cell counts of at least 350 cells/mm³ 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/mm³, or the viral suppression arm, in which they remained on antiretroviral therapy throughout the study.

Before the study was modified, patients in the conservation arm had spent 36% of the time on treatment, with a median of 18% of time on current interruptions in a one-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 cohort had 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/mm³, 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, 88% and 98% of the conservation and suppression patients, respectively, were on treatment, she said.

With respect to CD4 cells, the percent of time the conservation group spent with counts lower than 350 cells/mm³ fell from 31% before the study was modified to 23% at the time of follow-up. The time suppression group spent with counts lower than 350 cells/mm³ fell from 8% to 7%, Dr. El-Sadr reported.

Increased mortality was associated in the suppression group with an increased risk (OR 1.56). 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 1.5 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 because of the use of antiretroviral therapy throughout the trial,” she added. The findings, she said, support the recommendation against antiretroviral therapy interruption based on CD4 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. Powdery 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. Powdery said at the 15th Conference on Retroviruses and Opportunistic Infections. On enrollment in SUN, patients had baseline data on bone turnover, 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), 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 2.39) and CD4 count below 100 cells/mm³ (OR 2.10). Dr. Powdery 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. Powdery said at the meeting, which was sponsored by the Foundation for Retrovirology 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 a 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 treated without antiretroviral therapy (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 0.3%-1.5% 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 osteopenia and osteoporosis we are seeing in these patients is not a result of accelerated bone mineral loss but because for some reason we never reached the same peak mineralization as healthy individuals,” Dr. Powdery 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 determined, Dr. Mallal said that 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 (PRIDESCT) 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 HLA-B*5701 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 98%, 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 overall population, from the remainder,” Dr. Mallal said. “It was a 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 a shareholder for a company that has a patent pending for HLA-B*5701 testing.