Drug Changes May Reverse Lipoatrophy in HIV

Researchers will consider new combinations of drugs that may have favorable effects on fat distribution.

BY DIANA MAHONEY
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BOSTON — Switching antiretroviral medications can reduce the incidence and severity of drug-induced lipoatrophy in some HIV patients, according to three studies presented at a conference on retroviruses and opportunistic infections.

Subcutaneous fat loss, particularly from the face and limbs, is a frequent adverse effect of current combination antiretroviral therapy (ART) regimens. Although the effect has been associated with both nucleoside analogue reverse transcriptase inhibitors (NRTI) and protease inhibitors, not all of the drugs in both classes are equal in this regard, prompting investigators to consider new combinations that might have more favorable effects on fat distribution.

Switching to Abacavir or Tenofovir

In one study—a 48-week randomized, open-label trial—Graeme Moyle, M.D., of the Royal Free Hospital, London, and colleagues tested the hypothesis that removing a thymidine analogue from a highly active ART (HAART) regimen may improve associated lipoatrophy.

The investigators studied changes in limb fat as measured by dual energy x-ray absorptiometry (DXA) and visceral fat as measured by computed tomography in 105 HIV-infected adults in whom zidovudine (AZT, Retrovir) or stavudine (d4T, Zerit) therapy was replaced with either the nucleoside analogue abacavir (Ziagen) or the NRTI tenofovir (Viread).

Of the 71 stavudine and 34 zidovudine patients, 53 were randomly assigned to abacavir, and 52 were assigned to tenofovir. At 48 months, patients in both groups had similarly significant increases in leg and visceral fat from baseline, Dr. Moyle reported in an abstract presentation at the conference sponsored by the Foundation for Retrovirology and Human Health.

Among patients switched to abacavir, limb fat had increased at the end of the study by an average of 0.5 kg from a baseline average of 3.7 kg. In the tenofovir group, limb fat increased 0.3 kg from a baseline average of 3.9 kg. "Similar changes were observed in visceral and subcutaneous abdominal fat," Dr. Moyle said.

At 24 weeks, CT-measured limb fat among patients on the nucleoside-sparing regimen had increased 8%, while no change was noted in the abacavir group.

Both treatment groups maintained similar virologic suppression with the change in their regimens, although more patients in the abacavir group than in the tenofovir group discontinued therapy. Of the patients switched to abacavir, eight discontinued treatment, including three who developed hypersensitivity reactions. Three patients in the tenofovir arm dropped out of the study.

There were no statistically significant differences between treatment groups with respect to changes in bone mineral density scores, but measurements of mean changes in total cholesterol, LDL cholesterol, and triglycerides through week 48 significantly favored tenofovir.

Nucleoside-Sparing Regimens I

Mirroring these findings were the results from a prospective, randomized trial presented by Robert Murphy, M.D., of Northwestern University, Chicago on behalf of the AACTG 5110 Study Team.

In the first study to detect an improvement in lipoatrophy after only 24 weeks of treatment modification, 101 patients on zidovudine-inclusive or stavudine-inclusive regimens were randomized to either change their nucleoside to abacavir, switch to a nucleoside-sparing cocktail of ritonavir (Norvir)-boosted lopinavir (Kaletra) plus nevirapine (Viramune), or delay any switch until 24 weeks followed by randomization into one of the two treatment groups.

At 24 weeks, CT-measured limb fat among patients on the nucleoside-sparing regimen had increased 8%, while no change was observed in the abacavir group and a 3% increase was found in the treatment-delay group. Both treatment groups had significant increases in subcutaneous abdominal fat—17% for the nucleoside-sparing group and 9% for the abacavir group—compared with a decrease in the treatment-delay group. Visceral abdominal fat decreased in all three groups, with a smaller decrease in the nucleoside-sparing group than in the abacavir group (9% vs. 12%).

Virologic suppression was maintained in both treatment groups. "The [nucleoside-sparing] regimen led to a significant increase in CD4 cell count at 24 weeks," Dr. Murphy said, compared with a nonsignificant decrease with abacavir. Similar proportions of both treatment groups maintained undetectable viral loads.

Although statistically significant, "the 8% increase in limb fat from a very low baseline [median 18.9 cm^2] is modest and unlikely to be detected by the patient," Dr. Murphy noted. The investigators will present longer-term follow-up data, including quality of life assessments, later this year.

Nucleoside-Sparing Regimens II

Similar results were reported from a longer-term study in which 62 patients who had been on indinavir (Crixivan)/efavirenz (Sustiva) regimens for at least 18 months were randomly switched to either efavirenz and two nucleosides or to ritonavir-boosted lopinavir and efavirenz.

At baseline, median total limb fat for all patients, measured by DXA, was 6 kg. At 48 weeks, limb fat of patients in the nonnucleoside arm had increased significantly by a median of 562 g, compared with a 246-g loss in the nucleoside arm, reported lead investigator Pablo Tebas, M.D., of the University of Pennsylvania, Philadelphia.

At 48 weeks, there were no differences in amount of trunk fat, bone mineral density, or glucose metabolism between the treatment groups. However, total cholesterol and triglyceride levels increased significantly in the nonnucleoside group.

Follow-up data from 46 patients studied for a median of 104 weeks showed a median gain compared with baseline of 782 g of limb fat among the nonnucleoside patients and a median 900-g loss among patients receiving nucleosides.

Even though the median 13% gain in limb fat over 2 years represents a "relatively modest" increase, Dr. Tebas maintained that a switch to a nucleoside-sparing regimen is a valid therapeutic option for HIV patients with lipoatrophy. He warned, however, that the advantages of fat restoration must be weighed against the "inferior virologic potency" of nucleoside-sparing regimens.

Considering the poorly reversible nature of lipoatrophy as well as the fact that ART-induced changes in body-fat distribution can jeopardize the sustained effectiveness of and adherence to treatment, further research into the differences between specific antiretroviral agents within and between drug classes "is imperative," said plenary speaker Peter Reiss, M.D., of the Academic Medical Center in Amsterdam.

Additionally, insights gleaned from such research "must be allowed to benefit patients and HIV treatment programs worldwide," Dr. Reiss concluded. ■

Nearly Half of HIV-Positive Don't Get Recommended Therapy

BY DIANA MAHONEY
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BOSTON — Almost half of HIV-positive individuals in the United States who meet federal guidelines for antiretroviral therapy may not be receiving the treatment, according to a recent estimate by the Centers for Disease Control and Prevention.

Late diagnoses, unawareness of HIV risk factors and risk status, and treatment inaccessibility are among the likely factors contributing to the insufficient care of as many as 44% of the country's treatment-eligible HIV-positive individuals, CDC medical epidemiologist Eyasu Teshale, M.D., reported at a conference on retroviruses and opportunistic infections.

Using data from an analysis of AIDS diagnoses reported by all 50 states and HIV diagnoses reported by 30 states with well-established integrated HIV/AIDS reporting systems and lab-based CD4 reports, the CDC investigators estimated that, through 2003, there were about 480,000 treatment-eligible HIV/AIDS patients in this country.

Federal treatment guidelines advise antiretroviral therapy for HIV-infected patients with CD4 white blood cell counts of 350 cells/μL or lower; yet a statistical model estimates only 56% of eligible patients likely received it, said Dr. Teshale.

To estimate the number of HIV/AIDS patients receiving antiretroviral therapy, the CDC investigators extrapolated treatment percentages from CDC's Adult/Adolescent Spectrum of HIV Disease (ASD) project, a 10-city medical records–based surveillance project that prospectively collected information from more than 60,000 HIV/AIDS patients from 1990 through June 2004.

About 79% of the HIV-infected patients in the ASD population with CD4 counts below 350 cells/μL received antiretroviral therapy. "We applied that proportion to the 340,000 patients estimated to be 'in care' on a national level," Dr. Teshale said. Using this approach, the investigators estimated that 268,000 (79%) of the 340,000 patients diagnosed and receiving care in the U.S. received ART at the end of 2003. These 268,000 people represent only about 56% of the 480,000 Americans aged 15-49 who were living with HIV/AIDS and were eligible for ART at the end of 2003.

An estimated 42% of the eligible patients not getting antiretroviral therapy have not even been diagnosed with HIV infection, and as many as 25% are likely aware of their HIV status but are not receiving medical care for it, Dr. Teshale said at the conference, sponsored by the Foundation for Retrovirology and Human Health.

Among patients who have access to health care and are being treated for HIV, barriers to receiving the recommended antiretroviral treatment include the expense of multidrug cocktails, which can cost more than $10,000 a year. Although private insurance often covers this expense, patients receiving public health assistance are often placed on waiting lists for the drugs. Finally, some patients choose not to take the medications because of the side effects.

The new estimates, though limited by variations in data collection by states and inconsistencies in the medical records included in the analyses, support previous research demonstrating the unmet need for antiretroviral therapy.

The findings need to be validated by additional research, and the factors contributing to insufficient care for HIV-infected individuals deserve more study.

However, efforts to narrow the scope of the problem should be implemented without waiting for more research, Dr. Teshale said. These include increasing individuals' awareness of their HIV status, providing more effective methods for linking at-risk individuals to prevention and care programs, and encouraging health care providers to prescribe antiretroviral therapy, according to federal guidelines. ■