

Perspective

Diagnosis and Management of Body Morphology Changes and Lipid Abnormalities Associated With HIV Infection and Its Therapies

Body-shape changes and lipid abnormalities are common metabolic disorders in HIV-infected persons. It is likely that numerous factors contribute to body-morphology changes, including antiretroviral therapy, HIV infection itself, and immune reconstitution under antiretroviral therapy. A recent large cross-sectional investigation, the Fat Redistribution and Metabolism (FRAM) study, suggests that lipoatrophy is the most common feature of body-shape changes. Recent findings suggest modest benefit in reversing fat wasting by switching to abacavir from stavudine or zidovudine but no benefit from rosiglitazone treatment or switching from protease inhibitor to nonnucleoside reverse transcriptase inhibitor therapy. Human growth hormone treatment reduces fat accumulation, but treatment is expensive and gains in this regard are lost when treatment is stopped. Guidelines for treating lipid abnormalities in the non-HIV-infected population generally apply to HIV-infected persons; however, drug-drug interactions and overlapping toxicities between HIV and lipid therapies must be recognized. Although antiretroviral agents can raise lipid levels, there are data to suggest that in the case of cholesterol, HIV therapy reverses HIV infection-induced reductions of all cholesterol subsets. There are conflicting data regarding whether there is increased cardiovascular morbidity and mortality in the HIV-infected population. On balance, it appears that cardiovascular disease due to HIV-associated lipid disorders currently is a relatively infrequent problem, but one that is increasing in magnitude. This article summarizes a presentation by David A. Wohl, MD, at the February 2004 International AIDS Society–USA course in Atlanta.

Metabolic abnormalities in HIV-infected persons include lipodystrophy (ie, fat loss and fat accumulation) and lipid abnormalities that may pose risk of cardiovascular disease. A variety of factors may contribute to HIV-associated metabolic abnormalities; it has yet to be precisely determined to what relative degrees these abnormalities are due to HIV infection itself or to drugs used in treating HIV disease.

Body Morphology Changes

Case Presentation

A 37-year-old HIV-infected man on antiretroviral therapy presented with a complaint of progressive thinning of the face and legs and development of a “beer belly.” He has a 7-year history of HIV infection. His initial therapy was zidovudine/lamivudine/indinavir; stavudine was substituted for zidovudine after rapid development of anemia. His

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nadir CD4+ cell count was 364/μL, and his pretreatment plasma HIV RNA level is unknown. The indinavir regimen was modified to twice daily with ritonavir boosting 18 months ago. Currently, the patient has an HIV RNA level below assay detection limits and a CD4+ cell count of 1064/μL. Which among the following is a reasonable approach to addressing the body changes?

- Change stavudine to tenofovir or abacavir.
- Change indinavir/ritonavir to a nonnucleoside reverse transcriptase inhibitor (NNRTI) or atazanavir.
- Attempt to obtain human growth hormone therapy.
- Start treatment with metformin or a peroxisome proliferator-activated receptor (PPAR)-γ agonist (eg, rosiglitazone or pioglitazone).
- Stop antiretroviral treatment with the plan to restart it when the CD4+ cell count reaches a predetermined level (eg, 350/μL).

- Reassure the patient and forge on with the current successful regimen.

Discussion

Body morphology changes in HIV-infected persons include fat accumulation (lipohypertrophy) and fat loss (lipoatrophy). Fat accumulation includes dorsocervical fat accumulation (“buffalo hump”), visceral adiposity, and breast enlargement. Fat loss includes facial-fat and limb-fat loss. The Fat Redistribution and Metabolic Changes (FRAM) study has provided cross-sectional data on metabolic alterations in a large group of HIV-infected patients (Grunfeld, 2002 IAC; Gripshover, 10th CROI, 2003; Saag, 10th CROI, 2003; Zolopa, 10th CROI, 2003). Characteristics of a randomly selected population of more than 800 men and 350 women with HIV infection, of whom 14% were not receiving antiretroviral therapy, were compared with those of control subjects aged 33 to 45 years from a prospective cardiovascular disease cohort in the Coronary Artery Risk Development in Young Adults (CARDIA) database. Evaluations consisted of a self-report questionnaire, physical exam, dual energy x-ray absorptiometry (DEXA) scans, magnetic resonance imaging, computed tomography scans, and laboratory analyses.

Preliminary findings in HIV-infected men indicated that lipoatrophy is the main component of body morphology changes that distinguishes the HIV-infected group from the control group. Notably, despite clinical impressions to the contrary, those who reported fat loss did not have more central fat gain than control-group subjects, nor did they have increased visceral fat accumulation. There was no difference in the prevalence of buffalo hump between groups, but the size of the fat accumulation was significantly greater in the HIV-infected group than in the control

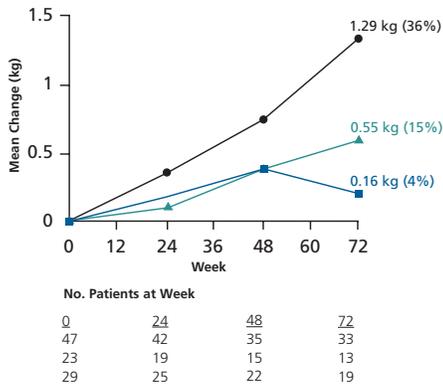


Figure 1. Changes in limb fat measured by dual-energy x-ray absorptiometry over 18 months in patients in the MITOX study who switched to abacavir at week 0 (circles) or week 24 (triangles) or who remained on stavudine- or zidovudine-containing regimens (squares) via on-treatment analysis. Adapted from Smith et al, 2nd IAS, 2003 and Martin et al, *AIDS*, 2004.

group. Findings in HIV-infected women indicated the presence of less peripheral fat than in control-group subjects (Shevitz, 2nd IAS, 2003). In contrast to what was observed in men, central lipoatrophy was inversely associated with peripheral lipoatrophy in women, and women without lipoatrophy had more upper trunk fat and more visceral adipose tissue than did controls. Some of the findings in men, such as the similarity in frequency of buffalo hump between patients and control-group subjects, do not appear to agree with the clinical experience of HIV care practitioners. A prospective follow-up of the FRAM study is under way that may help clarify the evolution of the body changes in HIV-infected men and women.

As noted, a variety of factors appear to play a role in body-shape changes. Available data support a direct role of nucleoside reverse transcriptase inhibitors (nRTIs), especially stavudine, in fat wasting, and a probable synergistic interaction with protease inhibitors (PIs) in this regard; evidence of a direct role of PIs in fat wasting is less clear. Cohort studies indicate that the duration of HIV disease is associated with body-shape changes, and other data indicate a potential role of immune reconstitution in these changes by showing a relation-

ship between body-shape changes and low CD4 + cell count nadirs. A potential role of genetic predisposition is suggested by findings indicating that patients' body mass index (BMI) is predictive of the tendency to gain or lose fat and possible racial and ethnic differences in the incidence of body-shape abnormalities.

Approaches under investigation for the treatment of fat accumulation include antiretroviral switching, exercise and diet, anabolic steroids, recombinant human growth hormone, metformin, PPAR- α agonists (glitazones), and plastic surgery. Approaches to fat loss, which can be considered the hallmark of the body-shape changes observed in HIV-infected patients, include antiretroviral switching, glitazones, and plastic surgery. A number of recent studies have examined some of these approaches to lipoatrophy. Switching of antiretroviral agents, which may be the approach best supported by currently available data, was assessed in the MITOX study, in which patients with peripheral lipoatrophy switched from stavudine or zidovudine to abacavir in their antiretroviral regimens. As shown in Figure 1, DEXA-measured limb-fat changes at 18 months increased by 36% in those switching to abacavir at week 0 and by 14% in those switching at week 24 (Smith, 2nd IAS, 2003). Subjects remaining on stavudine or zidovudine had a negligible 4% increase. The improvements observed with switching to abacavir are modest but at least indicate the potential for preventing worsening of fat loss.

The potential use of glitazones to treat HIV-associated lipoatrophy was suggested by the effects of the early glitazone troglitazone in producing peripheral fat gains in individuals with congenital lipoatrophy. A small randomized, placebo-controlled trial in 27 HIV-infected patients with insulin resistance and lipoatrophy indicated that treatment with rosiglitazone produced an overall significant increase in percentage of body fat at 3 months, as measured by bioelectrical impedance analysis (BIA; Hadigan et al, *Ann Intern Med*, 2004). Patients remaining on rosiglitazone or beginning rosiglitazone after 3 months reported greater satisfaction with body shape at 6 months. The amount of subcutaneous fat increased,

but there was little difference in limb fat. However, in a larger randomized, placebo-controlled trial (ROSEY study) in 108 patients, all of whom had lipoatrophy (mostly men, all white; Carr et al, *Lancet*, 2004), rosiglitazone treatment was not associated with improvements in DEXA-measured limb fat compared with placebo at 48 weeks. On this study, however, both the treatment and the control groups exhibited modest increases in limb fat — a finding that has yet to be explained. These negative results have dampened enthusiasm for the use of glitazones in this setting.

Studies using human growth hormone indicate that such treatment can reduce dorsocervical fat accumulation and visceral adiposity. Results of one study are shown in Figure 2 (Kotler, *JAIDS*, 2004). However, the treatment is expensive and rarely covered by third-party payors, and it is associated with numerous adverse effects including abnormal glucose metabolism, arthralgias, and carpal tunnel syndrome. In addition, body-shape abnormalities often return upon cessation. Moreover, since the agent is lipolytic, fat wasting can be worsened in

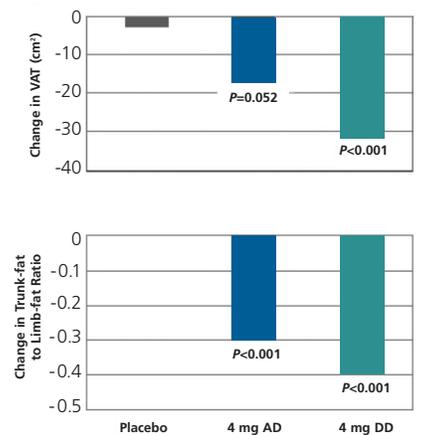


Figure 2. Changes in computed tomography measurement of visceral adipose tissue (VAT) and trunk-fat to limb-fat ratio measured by dual-energy x-ray absorptiometry in patients receiving recombinant human growth hormone treatment (intent-to-treat analysis). P values for change from baseline to week 12 compared with placebo group. DD indicates daily; AD, alternate days. Adapted from data in Kotler et al, *JAIDS*, 2004.

patients with both lipoatrophy and lipohypertrophy.

With regard to other potential approaches involving modification of antiretroviral therapy, one small study has suggested that switching from PI to NNRTI treatment has little effect on lipodystrophy (Garcia-Benayas, 5th Inter Workshop on ADR and Lipodystrophy, 2003). BIA and anthropometric assessment at 48 weeks in patients switching from a PI to nevirapine or efavirenz showed no changes in weight, BMI, lipodystrophy index, and other measures, and mild worsening of calf and triceps skin folds.

Among cosmetic approaches to lipoatrophy, polylactic acid injections have attracted considerable attention in some locales. Injection of the compound into subcutaneous tissue can result in improved appearance in cases of facial lipoatrophy. A recent report indicates that even in experienced hands, the procedure may be associated with serious adverse events in addition to pain and bruising in the injection area. In a study in 100 patients, an anaphylactic reaction to injection occurred in one patient and a facial nerve palsy occurred in another. However, this 2% serious adverse event rate is not so different from the adverse event rate seen with botulinum toxin injections. Polylactic acid injections are widely available in Europe, and there is interest in having the procedure approved for use in the United States.

Case Conclusion

The chosen approach in the case outlined above was to stop antiretroviral treatment, given that the patient's CD4+ cell count nadir was relatively high, and to restart it when the CD4+ cell count began to decrease toward 350/ μ L. Since the patient's pretreatment HIV RNA level is not known, the patient will be monitored for degree of viral rebound. The patient agreed with this approach. Had he expressed anxiety over stopping treatment, it is likely that the substitution of abacavir or tenofovir for stavudine would have been selected as the management option; in this case, the patient would have been informed that although dramatic improvement in the body morphology

was unlikely to occur at least in the short term, the approach would provide continued effective antiretroviral treatment and would likely prevent the lipodystrophy from worsening.

Lipid Abnormalities

Case Presentation

A 47-year-old man is newly diagnosed with HIV infection. His CD4+ cell count is 210/ μ L and his plasma HIV RNA level is 125,000 copies/mL. He agrees to initiate antiretroviral therapy. The patient smokes a pack of cigarettes per day, and does not have diabetes or hypertension. His father had a myocardial infarction (MI) at age 53 years. The patient's fasting lipid profile shows total cholesterol of 235 mg/dL, low-density lipoprotein (LDL) cholesterol of 141 mg/dL, high-density lipoprotein (HDL) cholesterol of 33 mg/dL, and triglyceride level of 290 mg/dL. In accordance with published guidelines and based on clinical efficacy and convenience, the patient is started on efavirenz/zidovudine/lamivudine and receives dietary counseling. A few weeks later, the patient is started on bupropion to assist in smoking cessation. At 4 months, the patient has a CD4+ cell count of 375/ μ L and HIV RNA level of less than 50 copies/mL. He has stopped taking bupropion, but his cigarette consumption is down to a half pack per day. His total cholesterol has increased to 248 mg/dL, LDL cholesterol to 147 mg/dL, and triglyceride level to 355 mg/dL; his

HDL cholesterol has increased to 38 mg/dL. Should the patient be put on lipid-lowering medication?

Discussion

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III provides guidelines for initiating lipid-lowering therapy in adults based on assessment of coronary risk (*JAMA*, 2001). In the absence of evidence to the contrary, these guidelines should be used in HIV-infected individuals. The LDL cholesterol level at which initiation of drug treatment is recommended and the target LDL cholesterol level are determined by number of coronary risk factors and level of 10-year risk for coronary disease as determined by the Framingham risk calculator. Although this patient has no clinically evident coronary disease, he has multiple risk factors, including older age, cigarette smoking, low HDL cholesterol, and family history of premature coronary disease. The Framingham point-scoring risk calculation shows the patient to have a 10-year coronary risk of approximately 25%, indicating that treatment should be considered at an LDL cholesterol level of 130 mg/dL or higher with a target of less than 100 mg/dL. It is important to note that based on studies of HIV-uninfected persons, the NCEP guidelines are being revised and will likely lower the threshold for lipid-lowering therapy initiation, a recommendation that will have implications for HIV-infected patients with dyslipidemia.

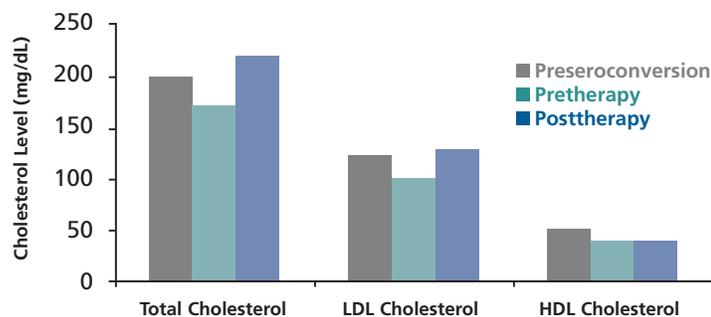


Figure 3. Total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol levels prior to HIV seroconversion (left, gray), prior to initiation of antiretroviral therapy (middle, green), and after initiation of therapy (right, blue) in patients in a Multicenter AIDS Cohort Study (MACS) cohort. Adapted from Riddler et al, *JAMA*, 2003.

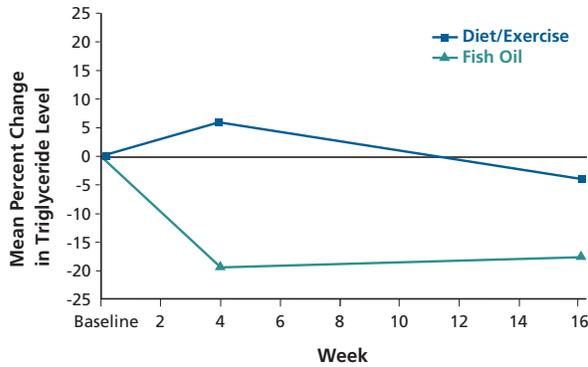


Figure 4. Effects of omega-3 fatty acids (fish oil) versus diet/exercise on triglyceride levels. Adapted with permission from Wohl et al, 11th CROI, 2004.

Manipulation of the antiretroviral regimen to include agents that may have less pronounced effects on blood lipids might be possible; however, changing the current regimen may not be desirable, since it continues to exert virologic control. Institution of lipid-lowering treatment is thus a reasonable approach.

Studies in healthy volunteers and HIV-infected patients have shown that antiretroviral drugs can raise lipid levels. However, it should also be noted that data from a Multicenter AIDS Cohort Study (MACS) indicate that HIV infection itself may be associated with decreases in total and LDL cholesterol. As shown in Figure 3, measurements of nonfasting blood samples from patients prior to HIV seroconversion, after infection but prior to potent antiretroviral therapy, and after the start of antiretroviral therapy suggest a decrease in cholesterol levels after seroconversion and an increase with potent antiretroviral therapy (Riddler, *JAMA*, 2003).

The effects of increased lipids on cardiovascular morbidity and mortality in the HIV-infected population remain incompletely defined. A retrospective analysis of the Veterans Administration database indicates that rates of hospital admission and death due to cardiovascular disease remained generally unchanged in HIV-infected patients between 1993 and 2001 (Bozzette, *N Engl J Med*, 2003). However, prospective data from a US and European cohort (D:A:D Study) indicate a significant association of rates of MI with years of combination antiretroviral therapy. On balance, available data appear to indicate that HIV-associated cardiovascular

disease is a relatively infrequent but probably growing problem and that patients with lipid risk factors should receive appropriate lipid-lowering therapy.

Case Conclusion

The patient was informed of his coronary risk status and was started on atorvastatin therapy to reduce LDL cholesterol level, with the statin selected to minimize the potential for harmful drug-drug interactions with antiretroviral drugs via cytochrome P450 isoenzyme metabolism. Recent data do indicate that efavirenz can induce the metabolism of atorvastatin and simvastatin, likely reducing the efficacy of these lipid-lowering agents (Gerber et al, 11th CROI, 2004). In practice this interaction may require cautious titration of the dose of atorvastatin if a suboptimal response is seen at starting doses. Statin treatment was well tolerated. The patient stopped smoking and lost 7 pounds with moderate exercise (walking every other day, taking stairs instead of the elevator) and dietary changes (fewer sweets, more fruits and vegetables). After 8 weeks, his LDL cholesterol level had been reduced to 123 mg/dL. Statin therapy rather than fibrate therapy was selected in this patient because of the patient's elevated LDL cholesterol level and the fact that reducing LDL cholesterol is the primary goal of lipid-lowering therapy in hypercholesterolemic patients. However, the patient also has an elevated triglyceride value. It has been demonstrated that omega-3 fatty acids can produce marked reduc-

tions in triglyceride levels in HIV-infected patients (Figure 4); given the patient's elevated triglyceride level, omega-3 fatty acid administration is also an option in this case.

Summary

HIV-associated body-shape changes are a vexing problem for which etiologies remain elusive and therapeutic options remain limited. Avoidance of or substitution for stavudine when possible appears to be a prudent measure to prevent or reduce lipoatrophy. Lipids are an important consideration when crafting antiretroviral therapies. The risk of coronary disease among HIV-infected persons appears to be relatively low at present but also appears to be increasing. The NCEP Adult Treatment Panel III guidelines for lipid lowering (www.nhlbi.nih.gov/guidelines/cholesterol) should be used in assessing an HIV-infected patient's need for lipid-lowering treatment.

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