HIV-Associated Lipoatrophy: What Are the Kinder, Gentler Agents?

Michael P. Dubé
Division of Infectious Diseases, Indiana University, Indianapolis

(See the article by Jemsek et al. on pages 273–80)

Lipoatrophy associated with antiretroviral treatment of HIV infection is a common and serious problem that is associated with significant aesthetic and metabolic derangements [1]. Clearly, therapy with thiazolidinediones or switching of therapy to nucleoside reverse-transcriptase inhibitors is suboptimal for addressing severe established lipoatrophy, so when possible, it is preferable to avoid or minimize this complication altogether by choosing the kinder, gentler antiretroviral agents. Because it is not clear whether fat accumulation, such as abdominal obesity, breast enlargement, and buffalo hump, is a complication associated with the use of particular drugs, I will limit my comments to the more definitively antiretroviral treatment–related morphologic complication of lipoatrophy.

Multiple lines of evidence from observational and randomized studies implicate nucleoside reverse-transcriptase inhibitors, particularly stavudine, in lipoatrophy. A recent randomized trial that compared stavudine versus tenofovir (either given in combination with lamivudine and efavirenz) reported greater limb fat levels (as determined by dual-energy x-ray absorptiometry [DEXA]) among tenofovir recipients at weeks 96 and 144 [2]. However, this study did not include baseline DEXA findings and thus could not evaluate the longitudinal patterns of fat changes over time or compare results during treatment with pretreatment status. Thus, it was not clear whether the overall pattern was one of gain or loss over time in this study, but the inferiority of stavudine was clear. In a substudy of a prospective, randomized trial that compared stavudine plus didanosine with zidovudine plus lamivudine (both given in combination with nelfinavir and/or efavirenz), subjects assigned to receive zidovudine and lamivudine had an increase in limb fat level from baseline (as determined by DEXA) of 4% at 64 weeks, whereas subjects assigned to receive stavudine and didanosine had a decrease of nearly 17% (P < .001, by between-groups comparison for overall change from baseline) [3]. Although the slight increase in limb fat level from the baseline level with zidovudine and lamivudine assignment at 64 weeks in this study is encouraging, longer-term data are needed to assess longer-term outcomes [4]. Regardless, differences between nucleoside reverse-transcriptase inhibitors are becoming clearer. Studies that compare tenofovir-, zidovudine-, and abacavir-based combination regimens are anxiously awaited. Existing clinical data are inadequate to speculate whether there are differences between those agents with regards to lipoatrophy.

HIV-1 protease inhibitors, when given in combination with nucleoside reverse-transcriptase inhibitors, may also be capable of contributing to lipoatrophy. There are conflicting data from observational studies with regard to the independent contribution of protease inhibitors to the development of lipoatrophy [4, 5]. Substitution of nonnucleoside reverse-transcriptase inhibitors for protease inhibitors has not been effective for treatment of established lipoatrophy. However, one randomized prospective study revealed greater limb fat loss with nelfinavir treatment, compared with efavirenz treatment, over 64 weeks [3]. However, the magnitude of the protease inhibitor effect in this study was smaller than the effect of nucleoside assignment.

In this issue of Clinical Infectious Diseases, in a substudy of a randomized trial of subjects with a CD4 cell count of ≥100 cells/mm³ whose initial antiretroviral therapy consisted of zidovudine and lamivudine plus either efavirenz or atazanavir [6], Jemsek et al. [7] report no evidence of lipoatrophy at 48 weeks of treatment. With both combinations, there was a small increase from the baseline level in both abdominal subcutaneous and limb fat levels that was not statistically significant, and...
there was an increase in the visceral fat level noted by CT. Although analysis of between-groups differences was not a primary objective, there appeared to be very similar effects with both efavirenz and atazanavir with regard to total and regional body fat changes. Consistent with the main study’s results [6], the new azapeptide protease inhibitor atazanavir had no significant effects on glucose or lipid measurements.

But do these results suggest a differential effect of atazanavir, compared with other protease inhibitors, on body fat changes? The metabolic effects of different protease inhibitors are often divergent; for example, indinavir causes early insulin resistance with relatively few lipid effects, and amprenavir causes significant lipid changes without early effects on insulin resistance [8]. Nelfinavir did not induce early insulin resistance, but it did have significant effects on lipids and limb fat [3]. Thus, a lack of atazanavir-based effects on lipid and glucose metabolism may not necessarily translate into kinder, gentler effects on subcutaneous fat. Unfortunately, a 48-week follow-up period may not be sufficient to detect more-subtle or delayed deleterious effects [4]. The time course of limb fat changes in initially antiretroviral-naive patients involves an early increase during the first 16–32 weeks of therapy. This increase occurs regardless of which drugs are used and is followed by variable stability or decrease over time [3, 4], which depends, at least in part, on the drugs being used [3]. This early increase in limb fat level, which may be more pronounced in patients with advanced HIV disease, can be lost as early as 48–64 weeks after the initiation of therapy. For example, I was a researcher in a study of regimens that contained didanosine and stavudine; in this study, the limb fat level had rapidly decreased at week 48 from week 16 peak values and was significantly lower than the level associated with zidovudine-lamivudine–containing regimens, but the level did not become significantly lower than the baseline level until week 64 [3]. Because no DEXA scans were included early in the study (i.e., weeks 16–24) by Jemsek et al. [7], it is possible that the limb fat findings reported at week 48 represented values that were significantly decreasing from earlier peak values that were not captured.

Although lower nadir CD4 cell count has not been confirmed as a risk factor for limb fat loss in prospective studies with serial longitudinal assessments, it and a number of other non–drug-related risk factors may also contribute to the risk of lipodystrophy [5]. Jemsek et al. [7] excluded subjects with a CD4 cell count of <100 cells/mm$^3$, thus possibly excluding patients who were at the greatest risk for lipodystrophy. To properly attribute a lack of lipodystrophy to atazanavir use, it will be important to study subjects for a longer period of time and to include data on subjects with lower CD4 cell counts.

The results reported by Jemsek et al. [7] are encouraging, particularly given that the effects on peripheral fat with the newer, glucose/lipid-friendly protease inhibitor atazanavir were comparable to those seen with efavirenz. Longer-term follow-up studies (i.e., those with a duration of >48 weeks) with a full range of entry CD4 cell counts are needed, as are studies of the body fat effects of ritonavir-boostered atazanavir therapy and direct comparisons with other protease inhibitors, before any unique peripheral fat-sparing effects of atazanavir can be confirmed.

Acknowledgments

Potential conflicts of interest. M.P.D. has been a consultant for Pfizer, GlaxoSmithKline, Gilead, and Bristol-Myers Squibb; has received donated drugs for research purposes from Bristol-Myers Squibb and Abbott; has received honoraria or been on the speakers’ bureau for Pfizer, GlaxoSmithKline, Gilead, and Bristol-Myers Squibb; and has received recent research funding from Bristol-Myers Squibb, TheraTec, and Serono.

References