Body Habitus Changes Related to Lipodystrophy

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Changes in body fat in persons infected with the human immunodeficiency virus (HIV) have been associated with deleterious changes in blood lipids and insulin resistance, raising concern that these changes will increase the risk for accelerated atherosclerosis. Changes in body fat are often identified in advanced disease but may also occur early after HIV infection is detected. Conflicting evidence suggests that fat maldistribution may be related to use of protease inhibitors, nonnucleoside reverse transcriptase inhibitors, or a combination of these two classes of drugs, but the etiologies of the various changes in body fat remain uncertain. To date there have been no remedies for the loss of subcutaneous fat, but recent evidence has suggested that discontinuation of stavudine or zidovudine therapy may be associated with limited restoration of extremity fat. For fat accumulation, a number of strategies have been attempted, including treatment with human growth hormone, androgens, or metformin, and changes in diet and exercise. As in persons not infected with HIV, it is expected that the cornerstone of management, especially in the presence of central obesity, dyslipidemia, and insulin resistance, will include a diet low in saturated fat, with low–glycemic index carbohydrates, and high in fiber. Very limited evidence in persons infected with HIV has suggested that a supervised exercise program may be beneficial.

From early in the era of HAART, a spectrum of changes in body fat have been reported to occur in 20%–80% of subjects receiving these therapies (table 1) [1, 2]. In those with abdominal obesity, hypertension, abnormal serum lipids, and evidence of insulin resistance, this constellation simulates features of the dysmetabolic syndrome (syndrome X) [3]. Moreover, there is also evidence that the loss of subcutaneous fat per se in persons with HIV is associated with insulin resistance [4–6]. Thus, there is concern that these disorders will increase the risk for accelerated atherosclerosis (coronary artery disease, stroke, and peripheral vascular complications), as occurs in other populations without HIV [7]. Here, I review the difficulties in ascertaining the incidence of body fat abnormalities, their relationship to antiretroviral therapies, and management of these complications.

INCIDENCE AND PREVALENCE

There are few data on the incidence of clinical fat maldistribution. One report describing 84 subjects from the French PRIMO cohort and who were initiating HAART (88% received at least one protease inhibitor [PI]) shortly after acute HIV infection indicated that the incidence of lipodystrophy was 5% at 6 months, 9% at 12 months, and 26% at 24 months [8]. These data suggest that changes in body fat may occur very early after HIV infection and are not limited to advanced disease. In a study of 494 consecutive antiretroviral therapy–naive subjects treated with 2 nucleoside reverse transcriptase inhibitors (NRTIs) and at least one PI from October 1996 to September 1999, the incidence of central obesity was 9.2 (95% CI, 7.0–11.4) and for lipoatrophy was 7.7 (95% CI, 5.7–9.7) per 100 patient-years (table 2) [9].

Most studies have been cross-sectional in design and initially reported disparate occurrence rates (table 1).
Table 1. Prevalence of fat loss and fat accumulation in patients with HIV related to PI therapy.

<table>
<thead>
<tr>
<th>Fat change</th>
<th>Incidence in patients with HIV who received</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PI therapy</td>
<td>No PI therapy</td>
</tr>
<tr>
<td>Fat loss, lipoatrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of facial fat</td>
<td>3/372 (1%)</td>
<td>2/63 (3%)</td>
</tr>
<tr>
<td></td>
<td>7/32 (22%)</td>
<td>7/29 (24%)</td>
</tr>
<tr>
<td></td>
<td>71/105 (68%)</td>
<td></td>
</tr>
<tr>
<td>Loss of extremity fat</td>
<td>9/116 (4%)</td>
<td>7/63 (11%)</td>
</tr>
<tr>
<td></td>
<td>4/32 (13%)</td>
<td>67/105 (64%)</td>
</tr>
<tr>
<td>Any fat wasting</td>
<td>72/368 (20%)</td>
<td>17/179 (9%)</td>
</tr>
<tr>
<td>Fat accumulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in dorsocervical fat</td>
<td>2/95 (2%)</td>
<td>0/32 (0%)</td>
</tr>
<tr>
<td></td>
<td>4/116 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/63 (5%)</td>
<td>0/42 (0%)</td>
</tr>
<tr>
<td></td>
<td>51/13 (38%)</td>
<td></td>
</tr>
<tr>
<td>Breast enlargement</td>
<td>3/372 (1%)</td>
<td>4/63 (6%)</td>
</tr>
<tr>
<td></td>
<td>5/116 (4%)</td>
<td>0/42 (0%)</td>
</tr>
<tr>
<td></td>
<td>35/95 (37%)</td>
<td>10/32 (31%)</td>
</tr>
<tr>
<td>Increased abdominal girth</td>
<td>3/272 (1%)</td>
<td>5/72 (7%)</td>
</tr>
<tr>
<td></td>
<td>19/116 (16%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13/63 (21%)</td>
<td>0/42 (0%)</td>
</tr>
<tr>
<td></td>
<td>53/95 (56%)</td>
<td>13/32 (41%)</td>
</tr>
<tr>
<td></td>
<td>68/105 (65%)</td>
<td></td>
</tr>
<tr>
<td>Any fat accumulation</td>
<td>9/13 (69%)</td>
<td>12/32 (38%)</td>
</tr>
<tr>
<td></td>
<td>50/368 (14%)</td>
<td>18/179 (10%)</td>
</tr>
<tr>
<td>Both fat loss and fat accumulation</td>
<td>5/272 (2%)</td>
<td>23/306 (8%)</td>
</tr>
<tr>
<td></td>
<td>21/116 (18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35/158 (22%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15/63 (24%)</td>
<td>0/42 (0%)</td>
</tr>
<tr>
<td></td>
<td>95/113 (84%)</td>
<td>1/28 (4%)</td>
</tr>
<tr>
<td></td>
<td>9/9 (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>172/368 (47%)</td>
<td>44/179 (25%)</td>
</tr>
</tbody>
</table>

NOTE. PI, protease inhibitor.

The wide variability in prevalence is likely related to the following causes: absence of standardized case definitions; inclusion of cases based on patients’ self-report of changes; variability in the way different physicians clinically assess fat distribution; and extraction of data from chart reviews. Several groups of national and international HIV investigators have assembled and attempted to develop clinically meaningful and relatively easy to apply case definitions for change in body fat that can be used for surveillance purposes. However, the reproducibility of such definitions has not been tested. Prospective longitudinal
studies with appropriate controls and objective, quantifiable
measurements of body fat (e.g., by dual X-ray absorptiometry
[DXA] and CT and MRI imaging) will be necessary to validate
case definitions, to reliably determine incidence, and to assess
the relationship among specific HIV treatments.

Four recent, larger studies (totaling nearly 5000 subjects)
describe patients experiencing fat maldistribution (table 2)
[10–13]. In the Aquitaine cohort from France [11], in which
patients’ fat maldistribution was diagnosed by treating clini-
cians, the prevalence was 38% among 581 subjects. The pre-
valence of fat wasting was 16%, fat accumulation 12%, and
mixed syndrome 10%. In a provinciwide Canadian report of
1035 participants [10], 50% of patients self-reported abnor-
malities of body fat, with 36% reporting fat wasting, 33% in-
creased abdominal girth, and 6% a buffalo hump. In the Lip-
dystrophy Italian Multicenter Study (LIMS) of 2258 subjects,
fat maldistribution was present in 33.2% of cases [12]. Finally,
in the HIV Outpatient Study (HOPS) cohort, 49% of 1077
subjects developed manifestations of fat maldistribution (13%
lipoatrophy, 13% fat accumulation, and 23% mixed syndrome)
[13]. These rates of lipodystrophy are lower (33%–50%) than
those reported earlier by Carr et al. [14] (83%) and emphasize
differences in methodologies, potential for selection bias, and
the need for reproducible case definitions.

### Table 2. Prevalence and incidence of fat loss and fat accumulation in patients with HIV.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. of subjects</th>
<th>Lipodystrophy, %</th>
<th>Lipoatrophy, %</th>
<th>Fat accumulation, %</th>
<th>Both lipoatrophy and fat accumulation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquitaine cohort [11]</td>
<td>581</td>
<td>38 (95% CI, 32–42)</td>
<td>16 (95% CI, 13–18)</td>
<td>12 (95% CI, 10–15)</td>
<td>10 (95% CI, 8–13)</td>
</tr>
<tr>
<td>LiMS cohort [12]</td>
<td>2258</td>
<td>33.2 (750a)</td>
<td>33.7 (253)</td>
<td>25.6 (192)</td>
<td>40.7 (305)</td>
</tr>
<tr>
<td>Canadian cohort [10]</td>
<td>1035</td>
<td>50</td>
<td>36</td>
<td>33b</td>
<td>NA</td>
</tr>
<tr>
<td>HOPS cohort [13]</td>
<td>1077</td>
<td>49</td>
<td>13</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Spanish cohort [9]</td>
<td>494</td>
<td>17c</td>
<td>11.7 (95% CI, 9.2–14.2)</td>
<td>9.2 (95% CI, 7.0–11.4)</td>
<td>7.7 (95% CI, 5.7–9.7)</td>
</tr>
</tbody>
</table>

**NOTE.** LIMS, Lipodystrophy Italian Multicenter Study; HOPS, HIV Outpatient Study; NA, not applicable.

a Proportion of 2258 with the abnormality.

b Increase in abdominal girth.

c Incidence per 100 patient-years.

**PATHOGENESIS AND ASSOCIATED RISK FACTORS**

**Female sex.** Trunk obesity rather than subcutaneous fat wast-
ing appears to occur more often in women than in men [5,
12, 15–17]. In the Aquitaine cohort, more than a quarter of
the subjects (n = 156) were women [11]. The prevalence of fat
maldistribution in these women was 37%, considerably greater
than the 10.5% prevalence in a smaller cohort reported earlier
[18]. In these women, fat wasting occurred less often (10%) com-
pared with men (17%), but fat accumulation was similar
between the sexes. In the large LIMS cohort, female sex was a
risk factor for combined fat loss and accumulation [12]. In the
Italian Cohort Naive Antiretrovirals (ICONA) study of anti-
retroviral therapy–naive subjects in which 704 women (27.9%)
were followed for a median of 96 weeks, female sex was a risk
factor for fat accumulation and for the mixed fat syndrome.
Likewise, in the prospective cohort from Spain, fat accumu-
lation was more likely to develop in women than in men [9].
Thus, it is possible that women may be at greater risk for
accumulation of fat, although a cross-sectional study evaluating
fat by a validated, reproducible methodology (i.e., DXA) in 265
subjects revealed no differences in occurrence of fat accumu-
lation or loss by sex [19]. Prospective studies will be necessary
to further evaluate whether there are true differences between
the sexes [20].

**PIs.** Initial reports of fat maldistribution suggested that
these changes were related to use of PIs. However, a sizable
portion of patients developing lipodystrophy had never received
a PI (table 1). In addition, a cross-sectional study involving
102 subjects (89 with and 13 without lipodystrophy) indicated
that subjects receiving PIs were no more likely to develop fat
loss or accumulation (the latter were assessed by CT scans)
than those not receiving a PI [21]. Results of a number of
switch studies in which PIs have been changed to non-NRTIs
have not demonstrated consistent, objective evidence of im-
provement in fat distribution 6–12 months after discontinuing
PIs (reviewed in [22]). It may be that favorable changes in body
composition take longer or that lipoatrophy is not reversible
in some patients. Finally, the well-documented effects of PIs
on lipid and carbohydrate metabolism may be independent of
changes in body fat [23].

Indirect evidence in fact did suggest that PIs were involved
because the odds of fat wasting were shown to increase with
the duration of therapy [14, 24–25]. The use of PIs also in-
creases the probability of intra-abdominal fat accumulation [14,
26]. Some of the most compelling evidence implicating PIs
emanates from a study that assessed a subset (n = 77) of 277
subjects undergoing serial DXA scans at 6-month intervals. In
that study, PI-based therapies were associated with a faster rate
of fat wasting than in subjects not receiving PIs [25]. In the
ments, which can result in considerable variability in outcomes.

However, this was a multicenter study and thereby

determined by skinfold measurement and physician assessment,

dine-indinavir regimen [34]. The occurrence of lipoatrophy, as

randomized to a stavudine- versus zidovudine-based lamivu-

study, follow-up was available after 30 months for 96 persons

contributed to the observed changes. Finally, in the NOV A VIR

Because there was no control group, these results should be

However, abdominal fat, as assessed by CT scans, also increased.

tonic measures improved after a median of 9 months [33].

In a report of 36 patients openly switched from stavudine

the subset for DXA scanning from the parent cohort were not

receiving stavudine than zidovudine after controlling for du-

the risk of lipoatrophy was 265% per year greater for patients

for >2 years was a risk factor for changes in body fat

NRTIs. Cross-sectional studies also suggest that the NRTIs

be causally related to changes in body habitus, possibly

by causing mutations in the mitochondrial DNA polymerase

gamma gene and thus adversely affecting mitochondrial oxida-

tive phosphorylation [27, 28]. The observation that older

subjects were more likely to have fat wasting [11, 13] supports

this concept because mitochondrial DNA mutations accumu-

late with aging. Length of therapy with NRTIs may also increase

the risk for fat loss [9, 13, 25, 29]. Finally, dual NRTI therapy

is more likely to cause fat wasting than is therapy with a single

NRTI [25].

There may be differences in the propensity of various NRTIs

to cause abnormalities of fat distribution. In the LIPOCO,

HOPS, Australian, and Swiss cohorts, treatment with stavudine

was a risk factor for lipoatrophy [17, 24, 25, 30–32]. Peripheral

fat wasting was also more common in subjects receiving sta-

vudine plus didanosine in the Swiss cohort [31]. Treatment

with lamivudine has also been associated with fat maldistri-

bution [21, 24]. These observations may reflect selection bias

because stavudine and lamivudine were the last NRTIs licensed

before the PIs, and their use may merely reflect previous use of

zidovudine or longer treatment with NRTIs.

However, when body fat was measured by serial DXA scans,

the risk of lipoatrophy was 265% per year greater for patients

receiving stavudine than zidovudine after controlling for du-

ration of NRTI usage and age [25]. The criteria for selecting

the subset for DXA scanning from the parent cohort were not

clear. In a report of 36 patients openly switched from stavudine
to abacavir or zidovudine, peripheral fat stores by anthropo-

metric measures improved after a median of 9 months [33].

However, abdominal fat, as assessed by CT scans, also increased.

Because there was no control group, these results should be

interpreted cautiously: uncontrolled interventions may have

contributed to the observed changes. Finally, in the NOVAVIR

study, follow-up was available after 30 months for 96 persons

randomized to a stavudine- versus zidovudine-based lamivu-
dine-indinavir regimen [34]. The occurrence of lipoatrophy, as
determined by skinfold measurement and physician assessment,
was significantly less common in subjects randomized to
zidovudine. However, this was a multicenter study and thereby
required different operators for the anthropometric measure-
ments, which can result in considerable variability in outcomes.

By contrast, in the Eurosupport II project, involving 1141

subjects, there was no difference in the occurrence of lipody-
strophy between subjects receiving stavudine and those receiving

lamivudine [35]. Similarly, in 98 heavily pretreated subjects,
stavudine was not more likely than zidovudine to be associated
with lipodystrophy [36]. Finally, in a German cohort of patients

who began HAART after 1 January 1996 and continued therapy

with either stavudine or zidovudine for a median follow-up of

23.8 months, there was no difference in the occurrence of lipody-
strophy after correction for confounding variables [37]. In the

prospective cohort study from Spain, no individual NRTI

was associated with increased risk [9]. Thus, it remains to be

established whether stavudine increases the risk of fat maldis-
tribution more than other NRTIs.

Combination antiretroviral therapy. It is also possible that

NRTI and PIs together contribute to abnormalities in fat dis-
tribution. Indeed, PI therapy combined with dual NRTIs re-
sulted in faster lipoatrophy than therapy with dual NRTIs,
whereas PI therapy per se did not exert a strong independent
risk for fat loss [25], although the predominance of data re-
viewed above suggests that PIs are causally related to lipody-
strophy. Moreover, in the Canadian study of 1035 subjects in

which PIs were associated with a nearly 3-fold increased risk
for lipodystrophy, stavudine and lamivudine were indepen-
dently associated with risk of lipodystrophy (OR, 1.35 and 1.32,
respectively) after adjustment for PI use [10]. Finally, in the

LIMS cohort of 2258 subjects, the risk was greater in subjects

treated with a combined regimen of NRTIs and PIs (OR, 2.1
[95% CI, 1.6–2.9]) compared with patients treated only with

NRTI and PIs together [12].

MANAGEMENT OF LIPOATROPHY

Little is known about options for management of lipoatrophy.

Anecdotal reports suggest that implants with collagen or fascia

in the buccal area improve facial appearance, but further loss
of fat may occur in some cases. Polylactic acid, a bioabsorbable
material that stimulates collagen formation, was injected in the

cheeks of 26 HIV-positive men who experienced fat wasting
[38]. Echography found that the mean dermal thickness in-
creased by 4.1 mm (151%) and 5.3 mm (196%) at weeks 12

respectively) after adjustment for PI use [10]. Finally, in the

LIMS cohort of 2258 subjects, the risk was greater in subjects

treated with a combined regimen of NRTIs and PIs (OR, 2.1
[95% CI, 1.6–2.9]) compared with patients treated only with

NRTI and PIs together [12].

Insulin sensitizing agents. Because both fat atrophy and

fat accumulation are associated with insulin resistance, which
are prone to insulin resistance from several different causes, early in the course of therapy [51]. Because persons with HIV abdominal obesity, growth hormone caused insulin resistance (insulin resistance) increased significantly and remained elevated. However, endogenous production of hepatic glucose (signifying in total fat, buffalo hump size, and visceral adipose tissue [53]. Because of the potential for liver toxicity and potential for drug interactions, controlled studies of thiazolidinediones in persons with HIV are needed before they can be recommended for treatment of lipodystrophy.

Treatment switching strategies. Although a number of switch studies in which PIs were changed to regimens without this class of drugs failed to demonstrate consistent, objective improvements in body composition, 3 recent reports indicated that changing stavudine to either zidovudine or abacavir resulted in small but statistically significant increases in subcutaneous fat, as assessed by DXA or CT scan [45–47]. Although these studies had limitations in design, they suggest that lipodystrophy may not be as irreversible as previously feared. Peer review will be important in understanding the validity and implications of these results.

MANAGEMENT OF FAT ACCUMULATION

Human growth hormone. Human growth hormone has potent fat-oxidizing properties and has decreased dorsocervical fat in persons with HIV [48–50] and reduced abdominal fat in HIV-negative men with abdominal obesity [51]. In 14 HIV-positive subjects with fat maldistribution treated with recombinant human growth hormone (rhGH; 6 mg/kg/d), body fat was significantly reduced after 24 and 36 weeks [52]. However, reaccumulation of central adipose tissue was nearly complete by 12 weeks after rhGH had been discontinued. Significant decreases in extremity fat also occurred during treatment, suggesting that rhGH may aggravate peripheral fat wasting. In a different study, 8 subjects with fat accumulation received rhGH (3 mg/d) for 6 months, which resulted in significant decreases in total fat, buffalo hump size, and visceral adipose tissue [53]. However, endogenous production of hepatic glucose (signifying insulin resistance) increased significantly and remained elevated at the end of the 6 months [54]. In HIV-negative subjects with abdominal obesity, growth hormone caused insulin resistance early in the course of therapy [51]. Because persons with HIV are prone to insulin resistance from several different causes, rhGH cannot be routinely recommended at the pharmacologic doses studied to date.

Androgens. In men without HIV who have had abdominal obesity, low or replacement doses with testosterone or similar synthetic analogues have reduced intra-abdominal fat, as assessed by CT scan [55]. The greatest beneficial effects occurred in men with lower levels of serum testosterone, as often occurs in men with HIV. Special care is needed in administering testosterone and its analogues to women, who appear to be more sensitive to developing insulin resistance in the setting of excess androgen. Moreover, as indicated above, treatment with androgens may also reduce peripheral fat [39, 40]. Thus, testosterone (or similar analogs) cannot be recommended at this time except in men who are overtly hypogonadal, with testosterone levels <250 ng/dL.

Metformin. Metformin is an insulin-sensitizing agent that reduces hepatic glucose production. In an open-label study in which metformin (850 mg) was administered 3 times a day to HIV-infected subjects with central obesity, fasting insulin levels and insulin response to oral glucose tolerance testing improved and visceral adipose tissue decreased [56]. In a placebo-controlled study of HIV subjects with lipodystrophy and impaired glucose tolerance, 26 subjects were randomized to placebo or 500 mg of metformin twice daily [57]. After 3 months, indirect measures of insulin sensitivity and glucose tolerance improved significantly, and there was a trend toward decreased visceral adipose tissue (change of 6%, P = .08). However, metformin, which may be complicated by lactic acidosis, cannot be recommended until additional controlled studies establish its relative efficacy and safety and the appropriate dose is determined for persons with HIV.

Diet and exercise. Until the efficacy and safety of pharmacological interventions are rigorously studied in persons with HIV, the cornerstone of management for central fat accumulation should be diet and exercise, as extrapolated from populations not infected with HIV [58]. For central fat accumulation, the goal should be to decrease intake of saturated fat and excess caloric energy. Aerobic exercise is expected to augment the effects of dietary change because intra-abdominal fat (mesenteric and omental adipose tissue) is metabolically more active than peripheral fat in responding to lipolytic stimuli, such as increases in epinephrine with exercise. In persons without HIV, intensive aerobic exercise can decrease intra-abdominal adipose tissue by 17%–20% [59]. In addition, aerobic exercise increases peripheral glucose disposal in obese persons, even in the absence of weight loss [60, 61], and should be beneficial for subjects with insulin resistance. A recent report suggests that an aerobic exercise program with a moderate-fat, low–glycemic-index, high-fiber diet can reverse aspects of lipodystrophy [62]. Supervised resistance (strength) training modestly decreased truncal fat as assessed by DXA scanning in 2
preliminary studies [63, 65], but resistance exercise is not expected to be as efficient in reducing fat as aerobic exercise. However, it remains to be determined whether vigorous aerobic exercise negatively affects peripheral fat stores in persons with HIV. Although the general goal for diet is caloric energy restriction to reduce central fat, the prescribing of specific changes for intake of macronutrients (fats and carbohydrates) should be based on serum lipid levels and glucose intolerance [64].

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