Current Perspectives on HIV-Associated METABOLIC and MORPHOLOGIC Abnormalities

A CME/CE-Certified Enduring Material: Monograph

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This activity is supported by an independent educational grant from Gilead Sciences Medical Affairs.
PROGRAM OVERVIEW
As the life expectancy of HIV patients increases due to better long-term management of HIV infection, there is also a higher incidence of metabolic and morphologic abnormalities among these patients. This CME activity will review data presented at a recently held conference on the causes and medical implications of the lipodystrophy syndrome in the HIV patient population.

TARGET AUDIENCE
This activity is intended for physicians, nurses, and other health care providers involved in the management of HIV-infected patients.

EDUCATIONAL OBJECTIVES
After completing this CME activity, participants should be able to:
• Discuss the metabolic and morphologic complications in HIV-infected patients on antiretroviral therapy
• Define the role of HIV treatment in the development of the lipodystrophy syndrome
• Describe how to manage the lipodystrophy syndrome with appropriate treatment, dietary changes, and lifestyle modifications

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Nelson Vergel, BSChE, MBA, volunteers his services as the director of the Program for Wellness Restoration (PoWeR). PoWeR has received unrestricted educational grants from Gilead Sciences, Inc; Roche Laboratories; Boehringer Ingelheim; Abbott Laboratories; and Pfizer Inc.

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This activity is jointly sponsored by Medical Education Collaborative and Healthmatters Communications.

This activity is supported by an independent educational grant from Gilead Sciences Medical Affairs.
Dear Health Care Professional:

The metabolic and morphologic complications common among patients with HIV pose significant clinical concerns. This is particularly true, given that these complications contribute to the risks for increased morbidity and mortality that naturally emerge in the general population as a result of the aging process. With the development of highly active antiretroviral therapy (HAART) more than 10 years ago, mortality from HIV/AIDS declined dramatically; the result is that people with HIV who are receiving treatment are now more likely to die from non–AIDS-related causes than from AIDS. Consequently, among people with HIV, the increased prevalence of metabolic complications (such as insulin resistance, diabetes, and dyslipidemia) and morphologic complications (such as lipoatrophy and lipohypertrophy) is a growing concern.

Lipodystrophy, and the body fat changes that accompany it, frequently receives the most attention from our patients because it can have such a devastating impact on their overall quality of life and feeling of well-being. As such, the emergence of body changes as a sign of underlying metabolic disease requires our ongoing attention. As clinicians who look after our patients’ long-term health, we take these concerns seriously.

One central, enduring issue is the need to more clearly define the relative contributions of HIV infection, antiretroviral therapy, and the aging process itself to the development of metabolic and morphologic complications. Such an understanding is essential both for developing strategies to treat these conditions and for designing antiretroviral regimens that might be able to prevent or reduce their emergence in HIV patients.

With further research, it will be possible to better understand the relative contributions that metabolic and morphologic syndromes make to comorbidities (eg, cardiovascular disease [CVD], diabetes, liver disease, kidney disease) that are the leading causes of morbidity and mortality in our patients. For example, although clinical data suggest that HAART exposure heightens CV risk, the proportion of CVD risk attributable to HAART remains substantially smaller than that attributable to classic CVD risk factors. It appears that as the mortality risk associated with HIV declines, caring for our HIV-infected patients will mean paying closer attention to the same health concerns that the overall population shares, but with an awareness of the added complexity that HIV infection brings.

The following monograph is based on material that was presented at a roundtable meeting of clinicians and advocates who are experts in the field of the metabolic and morphologic complications of HIV infection. It is our hope that this publication will raise the level of knowledge in this area by providing a thorough review of these complications, highlighting the role that HIV treatment plays in them, presenting an overview of the current state of research on these topics, and offering recommendations on the clinical management of lipodystrophy in HIV patients.

Sincerely,

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Clinicians working in the HIV field during the past decade and even longer have a unique perspective on the evolution of treatment for HIV and management of its complications. Their collective experience has been shaped by the history of the epidemic and the sudden and dramatic drop in AIDS deaths in the United States and Europe following the introduction of highly active antiretroviral therapy (HAART) in 1996. A recent update of the seminal paper by Palella and colleagues follows the trends in HIV treatment and mortality in the HIV Outpatient Study (HOPS) observational cohort since the introduction of HAART (Figure 1). Not surprisingly, the study found that HAART utilization rates increased from 43% of patients in 1996 to 82% in 2004. During the same time period, overall death rates among the HOPS cohort declined and remained low through 2004, while the proportion of deaths attributable to non–AIDS-defining illnesses (eg, hepatic, cardiovascular [CV]), and pulmonary disease, along with non–AIDS-related malignancies) continued to increase.

As a consequence of the sustained reduction in mortality among people living with HIV, clinicians have turned their attention to the long-term health of HIV patients and to key comorbidities such as cardiovascular disease (CVD), diabetes, liver and kidney disease, cancer, and neuropsychiatric illness. This change in focus is a testament to the remarkable effectiveness of HAART; however, the task of recognizing which comorbidities are related to HIV infection itself and its treatment and which are the result of the normal aging process remains a challenge.

This monograph examines the most important metabolic and morphologic changes that occur in HIV patients and how they can be effectively treated in concert with management of HIV disease. These metabolic dysfunctions and morphologic changes are broadly defined as dyslipidemia, insulin resistance, and body fat redistribution (Figure 2). Considering the prevalence of these conditions among HIV patients, the challenge remains to determine how these conditions are related to HIV disease and HAART. Clinicians have begun to clearly define the metabolic and morphologic changes associated with HIV, determine how they can be measured most accurately and consistently, understand the pathogenesis of these conditions, and assess their clinical relevance to patients. Continuing research will help clinicians make informed decisions as to the most effective ways to manage metabolic and morphologic conditions in their HIV patients.

These issues were explored in depth at a daylong roundtable meeting on August 18, 2007, in Boston. The meeting’s participants included high-level clinicians, researchers, and patient advocates, each of whom is considered an expert in the field of HIV therapy. Their insights into current research and strategies for successful HIV patient management are relevant to HIV treaters of all specialties.

**Figure 1.** Incidence of Mortality and HAART Usage Over Time

**Figure 2.** Factors in Metabolic Dysfunction in HIV Patients

---

*P* = .008 for trend.


HIV-ASSOCIATED METABOLIC ABNORMALITIES: AN OVERVIEW

Presented by Julian Falutz, MD

Pathogenesis

Theories of the pathogenesis of metabolic and morphologic abnormalities have evolved in the past several years. Early research suggested that only select classes of antiretroviral (ARV) agents were involved; now it is acknowledged that the picture is likely more complicated, with the potential involvement of numerous drug classes. The most rigorous scientific evidence has pointed to the impact of the protease inhibitors (PIs). For example, several of the PIs have been shown to interfere with the sterol-regulatory element-binding protein (SREBP)-1c, which regulates triglycerides (TGs), cholesterol, insulin, and adipocytes. Indinavir, in particular, may interfere with intranuclear activation factors that are required for the differentiation of peripheral adipocytes. This activity could theoretically explain some of the metabolic changes, including hypercholesterolemia, hypertriglyceridemia, and increased insulin resistance, that occur in HIV patients.

Data continue to accumulate which suggest the thymidine analogues (ie, stavudine and, to a lesser degree, zidovudine) may also decrease levels of SREBP-1c in HIV-positive patients treated with HAART. The AIDS Clinical Trials Group (ACTG) 5142 trial also revealed a possible association between efavirenz and lipoatrophy. Data from an in vitro study provide theoretical support for this observation in that SREBP-1c and peroxisome proliferator-activated receptor (PPAR)γ levels are decreased in cultured mouse and human preadipocyte cells treated with the drug.

Insulin Resistance

The contribution that PIs make to insulin resistance has been explored in studies of both HIV-negative and HIV-infected individuals. Results of studies in HIV-negative individuals have indicated that lopinavir/ritonavir and indinavir reduce peripheral glucose metabolism, thereby causing insulin resistance. In contrast, initial studies in HIV-infected patients have found no substantial change in insulin resistance from baseline with use of either atazanavir or saquinavir, indicating intraclass differences among PIs for this toxicity.

Data from the Metabolic Effects of Different Classes of Antiretrovirals (MEDICLAS) study suggest that patients treated with lopinavir/ritonavir plus nevirapine did not experience a decline in glucose disposal, whereas patients given lopinavir/ritonavir plus zidovudine and lamivudine experienced early and persistent insulin resistance, suggestive of thymidine analogue effects. These effects preceded any observed changes in body composition. Additional data on the metabolic effects of ARVs come from the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study, which evaluated the following 3 treatment strategies: PI plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) (n=141), non-nucleoside reverse transcriptase inhibitor (NNRTI) plus 2 NRTIs (n=141), or PI plus NNRTI plus 1 or 2 NRTIs (n=140). A particularly high rate of hyperinsulinemia was reported among those patients treated with a backbone of stavudine plus didanosine. No increase in insulin levels or insulin resistance was associated with a backbone of abacavir plus lamivudine. However, in a more recent update on this trial, it was shown that all treatment arms showed similar increases in plasma insulin levels. This outcome could be related to long-term drug effects or natural changes that occur with age.

The relationship between stavudine use and morphologic changes and/or abnormal insulin sensitivity has been further elucidated by recently published data. In HIV-negative subjects, 1 month of stavudine administration was associated with decreased insulin sensitivity and mitochondrial function, which occurred in the absence of body shape changes. Although stavudine use has decreased substantially in recent years, these data are valuable, eg, when considering potential treatment options in patients who may be at risk for developing diabetes. It also is important to recognize that stavudine use is still widespread in the developing world.

Cardiovascular Risk

Somewhat conflicting data suggest that HAART increases the risk for CVD in HIV patients. Several large studies have explored the relative contributions that HIV infection, antiretroviral therapy (ART), and traditional CVD risk factors make to risk in various HIV patient populations.

D:A:D

Recently published results from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study indicate that an increased incidence of myocardial infarction (MI) is associated with PI therapy (relative rate of MI per year of PI therapy = 1.16). Earlier data from the D:A:D study indicated an association between combination ART and MI; in contrast, the more recent analysis reveals no association between NNRTI treatment and increased risk of MI, although there were fewer person-years of data for the NNRTI class (52,457 versus 72,846 for the PIs).

It has been argued that despite a possible increase in CV risk associated with some of the older PIs, it is offset by the benefit of decreased CV risk associated with controlling HIV infection.
In addition, it is possible to speculate that the increase in CV risk with long-term exposure to PIs is actually an effect of aging in the HIV patient population (even though the D:A:D study controlled for age in its analyses). The results of the D:A:D study also suggest that HAART exposure makes up a substantially smaller proportion of CV risk than do classic CV risk factors, such as previous CVD or current or former smoking (Figure 3).\textsuperscript{17}

**SMART**

The Strategies for Management of Anti-Retroviral Therapy (SMART) trial, which randomized 5472 patients, compared continuous with intermittent HAART based on CD4 cell counts. Data analysis revealed a borderline significant increased risk for CV events in patients in the intermittent treatment arm (Table 1). The SMART study also showed a decline in total and low-density lipoprotein (LDL) cholesterol in the intermittent treatment arm, along with a decline in high-density lipoprotein (HDL) cholesterol, compared with the continuous treatment arm.\textsuperscript{18}

**Veterans Affairs Quality Enhancement Research Initiative for HIV**

The Veterans Affairs Quality Enhancement Research Initiative for HIV was a large retrospective study of the risk of CV and cerebrovascular disease that studied 36,766 patients who received care for HIV infection at Veterans Affairs facilities between January 1993 and June 2001. Of these patients, 70.2% received nucleoside analogues, 41.6% received PIs, and 25.6% received NNRTIs for a median of 17 months, 16 months, and 9 months, respectively. Between 1995 and 2001, the rate of admissions for CV or cerebrovascular disease decreased from 1.7 to 0.9 per 100 patient-years, and the rate of death from any cause decreased from 21.3 to 5.0 deaths per 100 patient-years. Patient-level regression analyses indicated that there was no relation between the use of NRTIs, PIs, or NNRTIs on the one hand and the hazard of CV or cerebrovascular events on the other.\textsuperscript{19}

**Metabolic Syndrome: More Common in HIV Patients?**

Evidence from a number of studies does not overwhelmingly support the idea that the metabolic syndrome occurs more frequently in treated HIV-infected populations than in controls.\textsuperscript{20-23} Instead, prevalence estimates are similar to those in the general population, ranging from 20% to 30%.

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### Table 1. SMART Study: Cardiovascular Events\textsuperscript{18}

<table>
<thead>
<tr>
<th>CV Events</th>
<th>Number of Events in the Intermittent Treatment Group</th>
<th>Number of Events in the Continuous Treatment Group</th>
<th>Relative Hazard: Intermittent/Continuous (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical MI, silent MI, stroke, CAD requiring invasive procedure or surgery, death from CVD</td>
<td>48</td>
<td>31</td>
<td>1.57 (1.00 – 2.46)</td>
<td>.05</td>
</tr>
<tr>
<td>Clinical MI, silent MI, stroke, CAD requiring invasive procedure or surgery, death from CVD + Peripheral vascular disease, CHF, CAD requiring drugs</td>
<td>76</td>
<td>52</td>
<td>1.49 (1.04 – 2.11)</td>
<td>.03</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure.

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**Antiretroviral Therapy and Dyslipidemia**

Presented by Esteban Martinez, MD

Current ART regimens usually consist of a combination of at least 3 drugs: a backbone of 2 nucleoside or nucleotide analogues and a third drug that is most commonly an NNRTI or a PI. To date, studies have not found a benefit to giving initial regimens that include more than 3 drugs (excluding boosted PIs). However, as new agents and classes enter the market, the current 3-drug approach may evolve.

All 3 primary classes of ARV drugs are associated with lipid abnormalities in HIV patients, including PIs, NNRTIs, and NRTIs (Table 2). However, not all lipid changes in patients being treated for HIV infection are related to ARV drugs. Hypertriglycerideremia is a common lipid alteration among untreated HIV patients—especially as CD4 cell counts decrease. Increases in LDL cholesterol are often a result of health restoration following the initiation of ART, rather than a drug effect, since these increases are not observed in HIV-negative subjects. Some ARVs do seem to have consistent effects; elevated TG levels, for example, are observed in association with ritonavir, independent of HIV serostatus. Other studies have shown that both low- and high-dose ritonavir have been associated with increased plasma levels of total cholesterol, and particularly TGs, in HIV-negative subjects.

**Table 2. Potential Lipid Effects of Select ARVs**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>LDL</th>
<th>TG/VLDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>RTV</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>IDV</td>
<td>↑↔</td>
<td>↔↑</td>
<td>↔↑</td>
</tr>
<tr>
<td></td>
<td>APV</td>
<td>↑</td>
<td>↔↑</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>NFV</td>
<td>↑</td>
<td>↔↑</td>
<td>↔↑</td>
</tr>
<tr>
<td></td>
<td>ATV</td>
<td>↔</td>
<td>↔↑</td>
<td>↑</td>
</tr>
<tr>
<td>NNRTI</td>
<td>EFV</td>
<td>↑</td>
<td>↑↔</td>
<td>↔↑</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
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<td>↔</td>
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<tr>
<td>NRTI</td>
<td>d4T</td>
<td>?↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td></td>
<td>TDF</td>
<td>↔↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

*Full-dose ritonavir.

ARVs, antiretrovirals; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; PI, protease inhibitor; RTV, ritonavir; LPV/r, ritonavir-boosted lopinavir; IDV, indinavir; APV, amprenavir; NFV, nefilnavir; ATV, atazanavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; EFV, efavirenz; NVP, nevirapine; NRTI, nucleoside reverse transcriptase inhibitor; d4T, stavudine; TDF, tenofovir.

**Lipid Effects of Antiretroviral Agents**

The PIs have long been considered to have the greatest impact on lipids. However, it is clear that members of the NNRTI and NRTI classes can also have significant impact on lipid metabolism in HIV patients. In Table 3a, page 8, data from several studies involving PIs and NNRTIs demonstrate the effects of members of these 2 ARV classes on lipid metabolism. Table 3b, page 10, presents results of trials that examined the lipid effects of select NRTIs. Some of these trials illustrate how switching to regimens that have less potential to alter lipid metabolism can improve patients’ lipid profiles.

Lipid effects of PIs are clearly demonstrated in the trials summarized in Table 3a. Ritonavir-boosted PIs consistently result in elevations of total cholesterol (TC), LDL, and TGs. It appears that the presence of the boosting dose of ritonavir is more likely to be responsible for the increases in TGs, while the other PI is less likely to be the causative agent. Atazanavir appears to have significantly less negative impact on lipid profiles than boosted PIs; however, when it is boosted with ritonavir, these positive effects are somewhat mitigated.

The studies that examined the effects of NNRTIs on lipids were interesting in that intraclass differences were revealed for nevirapine and efavirenz. The 2NN trial showed that efavirenz increased TG levels significantly more than nevirapine, while nevirapine was associated with a significantly greater increase in HDL. The ACTG 5142 trial demonstrated, somewhat paradoxically, that combining an NNRTI (efavirenz) with a ritonavir-boosted PI (lopinavir) results in additive negative effects on TC and TG levels and additive positive effects on HDL. The NEFA switch study showed that replacing a PI with either a NRTI (abacavir) or an NNRTI (nevirapine or efavirenz) can significantly improve lipid profiles, especially reducing TC and increasing HDL.

The studies comparing the lipid effects of NRTIs demonstrate unequivocally that stavudine has a highly significant negative impact on patients’ lipid profiles. Switch studies GS 903E and RECOVER, not shown in table, have shown that replacing stavudine with tenofovir greatly improved lipid parameters, particularly TC and TGs. Patients switched to tenofovir also had better lipid responses compared to patients switched to abacavir from a thymidine analogue. Another switch study, Simplification With Easier Emtricitabine and Tenofovir Study (SWEET), showed that patients switched to the combination of tenofovir/emtricitabine fared better than those who remained on ziduvidine/lamivudine, particularly with respect to TC and TG levels.
### Study Name: BMS 034

**Study design**
The BMS 034 study was a randomized, double-blind, active-controlled study comparing the efficacy and safety of ATV versus EFV in treatment-naïve patients.

Patients were randomized to receive either ATV 400 mg QD or EFV 600 mg QD, each with fixed-dose ZDV/3TC BID.

At 48 weeks:
- ATV: n=339
- EFV: n=322

Reference: Squires *J Acquir Immune Defic Syndr* 2004

**Results**
Percent change from baseline in mean lipid parameters at 48 weeks:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV (%)</th>
<th>EFV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>+2%</td>
<td>+21%</td>
</tr>
<tr>
<td>LDL</td>
<td>−1%</td>
<td>+18%</td>
</tr>
<tr>
<td>HDL</td>
<td>+13%</td>
<td>+24%</td>
</tr>
<tr>
<td>TGs</td>
<td>−9%</td>
<td>+23%</td>
</tr>
</tbody>
</table>

*P < .0001 vs EFV

### Study Name: 2NN

**Study design**
The open-label 2NN study examined lipid changes in 1216 patients following treatment with NVP, EFV, or both, in combination with d4T and 3TC.

At week 48:
- NVP: n=417
- EFV: n=289


**Results**
Percent change from baseline in mean lipid parameters at 48 weeks:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NVP (%)</th>
<th>EFV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>+27%</td>
<td>+31%</td>
</tr>
<tr>
<td>LDL</td>
<td>+35%</td>
<td>+40%</td>
</tr>
<tr>
<td>HDL</td>
<td>+42%</td>
<td>+34%</td>
</tr>
<tr>
<td>TGs</td>
<td>+20%</td>
<td>+49%</td>
</tr>
</tbody>
</table>

*P = .036 for the difference between NVP and EFV

### Study Name: BMS 044

**Study design**
The BMS 044 study was a multinational, open-label, switch study to determine the long-term efficacy and safety of ATV 400 mg QD in patients previously treated with ATV or NFV plus d4T and 3TC in the BMS AI424-008 study.

At 24 weeks:
- NFV→ATV: n=69

Reference: Wood *J Acquir Immune Defic Syndr* 2004

**Results**
Percent change from baseline in mean lipid parameters in NFV→ATV patients at 24 weeks:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV (%)</th>
<th>EFV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>−16%</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>−20%</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>+5%</td>
<td></td>
</tr>
<tr>
<td>TGs</td>
<td>−25%</td>
<td></td>
</tr>
</tbody>
</table>

*P < .0001

### Study Name: NEFA

**Study design**
NEFA was a randomized trial designed to compare the efficacy of NVP, EFV, or ABC as substitutes for the PI in a patient’s current regimen.

A subset of 90 patients constituted the metabolic substudy of NEFA.

At month 24:
- ABC: n=22
- EFV: n=21
- NVP: n=26

Reference: Fisac *AIDS* 2005

**Results**
Percent change from baseline in median lipid parameters at 24 months:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ABC (%)</th>
<th>EFV (%)</th>
<th>NVP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>−11%</td>
<td>−7%</td>
<td>0%</td>
</tr>
<tr>
<td>HDL</td>
<td>+5%</td>
<td>+18%</td>
<td>+34%</td>
</tr>
<tr>
<td>TGs</td>
<td>+2%</td>
<td>−14%</td>
<td>−28%</td>
</tr>
</tbody>
</table>

*P < .001 vs baseline

Current Perspectives on HIV-Associated **METABOLIC and MORPHOLOGIC Abnormalities**
### Study Name: BMS 045

#### Study design

The BMS 045 study was an open-label, randomized, multinational trial comparing the efficacy and safety of LPV/r with ATV/RTV in treatment-experienced patients.

Patients were randomized to receive either LPV/r 400 mg/100 mg BID or ATV/RTV 300 mg/100 mg QD, each with TDF 300 mg QD and one additional NRTI.

At 96 weeks:
- LPV/r: n=65
- ATV/RTV: n=67

Reference: Johnson AIDS 2006

#### Results*

Percent change from baseline in median lipid parameters at 96 weeks:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV/RTV</th>
<th>LPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>−7%</td>
<td>+9%a</td>
</tr>
<tr>
<td>LDL</td>
<td>−11%</td>
<td>+1%</td>
</tr>
<tr>
<td>HDL</td>
<td>−5%</td>
<td>+7%</td>
</tr>
<tr>
<td>TGs</td>
<td>−2%</td>
<td>+30%a</td>
</tr>
</tbody>
</table>

^ aP < .0001 vs ATV/RTV

### Study Name: SWAN

#### Study design

BMS 097 or SWAN was a 48-week, open-label, switch trial involving HIV-positive patients with stable PI-based regimens and virologic suppression (with or without RTV).

Patients were randomized 2:1 to switch to an ATV-based regimen (ATV 400 mg QD or ATV/RTV 300/100 mg QD) or continue to receive their existing PI.

At week 48:
- ATV group: n=230
- Comparator PI group: n=105

Reference: Gatell Clin Infect Dis 2007

#### Results*

Percent change from baseline in mean lipid parameters at 48 weeks:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ATV group</th>
<th>Comparator PI group</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>−15%a</td>
<td>−3%</td>
</tr>
<tr>
<td>LDL</td>
<td>−12%</td>
<td>−5%</td>
</tr>
<tr>
<td>HDL</td>
<td>−1%</td>
<td>−3%</td>
</tr>
<tr>
<td>TGs</td>
<td>−33%a</td>
<td>+9%</td>
</tr>
</tbody>
</table>

^ aP < .0001 vs comparator PI group

### Study Name: ACTG 5142

#### Study design

ACTG 5142 was an open-label, randomized trial that compared the following class-sparing regimens for naïve subjects: LPV/r + EFV vs LPV/r + 2 NRTIs vs EFV + 2 NRTIs.

NRTIs were selected before randomization: ZDV, d4T, or TDF plus 3TC.

At week 96:
- EFV: n=190
- LPV/r + EFV: n=189

Reference: Haubrich 14th CROI 2007 Abstract 38

#### Results*

Percent change from baseline in mean lipid parameters at 96 weeks:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EFV</th>
<th>LPV/r</th>
<th>LPV/r + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>+21%a</td>
<td>+21%a</td>
<td>+37%</td>
</tr>
<tr>
<td>HDL</td>
<td>+26%a</td>
<td>+23%a</td>
<td>+46%</td>
</tr>
<tr>
<td>TGs</td>
<td>+12%a</td>
<td>+41%c</td>
<td>+54%</td>
</tr>
</tbody>
</table>

^ aP < .01 vs LPV/r + EFV
^ bP < .01 vs LPV/r
cP = .025 vs LPV/r + EFV

*Percent changes from baseline in mean or median lipid parameters were calculated using the following equation:

(lipid parameter value [week X]) − (lipid parameter value [baseline]) / (lipid parameter value [baseline]) × 100.

ATV, atazanavir; EFV, efavirenz; QD, once daily; ZDV, zidovudine; 3TC, lamivudine; BID, twice daily; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; 2NN, 2 nonnucleoside study; NVP, nevirapine; d4T, stavudine; NFV, nelfinavir; NEFA, Nevirapine, Efavirenz, and Abacavir study; ABC, abacavir; LPV/r, lopinavir/ritonavir; RTV, ritonavir; SWAN, Switch to ANother protease inhibitor study (BMS 097); CROI, Conference on Retroviruses and Opportunistic Infections.
### Table 3b: Lipid Parameters in NRTI Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>GS 903</th>
<th>Study design</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prospective, randomized, multinational, double-blind trial designed to evaluate the efficacy and safety of TDF versus d4T in treatment-naïve patients.</td>
<td>Percent change from baseline in mean lipid parameters at 48 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients were randomized to receive TDF 300 mg QD (n=299) or d4T 40 mg BID (n=303), with placebo, in combination with 3TC 150 mg BID and EFV 600 mg QD.</td>
<td>TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At week 144:</td>
<td>TDF: +21%a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF: n=217</td>
<td>LDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>d4T: n=201</td>
<td>TDF: +9%a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference: Gallant JAMA 2004a</td>
<td>HDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF: +9%b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference: Gallant JAMA 2004a</td>
<td>TGs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF: +2%a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Name</th>
<th>RAVE</th>
<th>Study design</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RAVE was an open-label, comparative study in which patients with lipoatrophy were switched from a thymidine nucleoside analogue to either TDF or ABC.</td>
<td>Percent changes from baseline in mean lipid parameters at 48 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At 48 weeks:</td>
<td>TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF: n=52</td>
<td>TDF: −8%a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABC: n=53</td>
<td>LDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF: −8%b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference: Moyle AIDS 2006a</td>
<td>HDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF: −8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference: Moyle AIDS 2006a</td>
<td>TGs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF: −16%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Name</th>
<th>GS 934</th>
<th>Study design</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>The GS 934 study was a randomized, open-label noninferiority trial examining the efficacy and safety of TDF plus FTC and EFV versus ZDV/3TC plus EFV, in treatment-naïve patients.</td>
<td>Percent change from baseline in mean lipid parameters at 144 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At week 144:</td>
<td>TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF + FTC: n=157</td>
<td>TDF + FTC: +15%a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZDV/3TC: n=125</td>
<td>TGs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF + FTC: +3%b</td>
</tr>
</tbody>
</table>
|            |        | Reference: Arribas 4th IAS 2007 Poster WEPEB029a | *
|            |        |              | P <.005 vs ZDV/3TC | P =.047 vs TDF + FTC |

<table>
<thead>
<tr>
<th>Study Name</th>
<th>SWEET</th>
<th>Study design</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>In the SWEET study, patients were randomized to either continue receiving ZDV/3TC + EFV or be switched to TDF/FTC + EFV.</td>
<td>Percent changes from baseline in median lipid parameters at 24 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At 24 weeks:</td>
<td>TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC: n=117</td>
<td>TDF/FTC: −7%a,b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZDV/3TC: n=117</td>
<td>LDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF/FTC: −3%c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference: Moyle 4th IAS 2007 Abstract WEPEB028a</td>
<td>HDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF/FTC: −2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference: Moyle 4th IAS 2007 Abstract WEPEB028a</td>
<td>TGs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF/FTC: −2%a,d</td>
</tr>
</tbody>
</table>

*Percent changes from baseline in mean or median lipid parameters were calculated using the following equation: (lipid parameter value [week X] – lipid parameter value [baseline]) / lipid parameter value [baseline] × 100.

TDF, tenofovir; d4T, stavudine; QD, once daily; BID, twice daily; 3TC, lamivudine; EFV, efavirenz; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; RAVE, Randomized Abacavir versus Viread Evaluation study; ABC, abacavir; FTC, emtricitabine; ZDV, zidovudine; IAS, International AIDS Conference; SWEET, Simplification With Easier Emtricitabine and Tenofovir study.
Lipid Effects of Newer Antiretrovirals

Data on the metabolic effects of recently approved or soon to be approved ARV drugs are limited. However, it is important that clinicians have as much information as possible on how these new drugs are likely to affect the metabolic status of HIV patients, in order to make effective clinical management decisions.

**Darunavir and Tipranavir**

The newest PIs, darunavir and tipranavir, were FDA approved in March 2007 and June 2005, respectively. They are both indicated for use with ritonavir boosting, in combination with other ARVs, to treat HIV infection in heavily treatment-experienced adults who have drug resistance to multiple PIs.

In the POWER 1 and 2 trials, treatment-experienced patients were randomized to receive darunavir/ritonavir or a comparator PI regimen. At 48 weeks, darunavir/ritonavir had similar effects on lipids as the comparator PIs (primarily lopinavir/ritonavir) used in this population of patients requiring salvage therapy. In the ARTEMIS trial was a randomized, open-label study designed to compare the efficacy and safety of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve patients. Patients were randomized to receive 1 of 2 regimens for 96 weeks: (1) darunavir/ritonavir (800 mg/100 mg once daily) plus tenofovir 300 mg and emtricitabine 200 mg once daily or (2) lopinavir/ritonavir (400 mg/100 mg twice daily or 800 mg/200 mg once daily) plus tenofovir 300 mg and emtricitabine 200 mg once daily. At 48 weeks, the darunavir/ritonavir group experienced a lower incidence of lipid abnormalities (particularly regarding TGs) than the lopinavir/ritonavir group, consistent with the dose-dependent effect of ritonavir.

Tipranavir/ritonavir’s (500 mg/200 mg twice daily) efficacy and safety were compared with those of comparator PI-based regimens plus optimized background therapy in 2 nearly identical trials, RESIST 1 and 2 (Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir), in heavily pretreated patients. Compared with patients receiving comparator PI regimens, a greater number of tipranavir/ritonavir-treated patients had grade 3-4 elevations in cholesterol and triglyceride levels in both trials. It is likely that the higher dose of ritonavir (400 mg per day) than is typically given is at least partly responsible for these results.

**Enfuvirtide**

Enfuvirtide, a fusion inhibitor, was approved in October 2004 and is indicated for the treatment of HIV infection in combination with other ARVs in treatment-experienced patients. In a double-blind, placebo-controlled, crossover study in healthy, HIV-negative volunteers (N=17), enfuvirtide had no significant effect on lipid levels or other markers of metabolic toxicity (eg, changes in mitochondrial DNA, insulin sensitivity, or lactate).

**Maraviroc**

In August 2007, maraviroc became the first approved drug in the CCR5-inhibitor class. Detailed data on the lipid profiles of patients treated with maraviroc in the MOTIVATE 1 and 2 trials are not yet available. However, the National Pharmacy Benefits Management Drug Monograph for maraviroc notes that patients treated with the drug had greater elevations in cholesterol, LDL, and triglycerides than did those in the placebo group.

**Raltegravir**

Raltegravir, an integrase inhibitor, was approved in October 2007 for the treatment of HIV infection in treatment-experienced patients in combination with other ARVs.

BENCHMRK 1 and 2 (Blocking Integrase in Treatment Experi- enced Patients with a Novel Compound Against HIV: MeRK Study) are ongoing multicenter, triple-blind, randomized studies designed to evaluate the efficacy and safety of raltegravir in HIV patients with triple-class-resistant virus. In these studies, patients have been randomized to receive either twice-daily raltegravir (400 mg) plus optimized background therapy (OBT), or placebo plus OBT. Data from 24 weeks suggest that in the salvage setting, raltegravir has a lipid profile comparable with the placebo arm.

Another multicenter, double-blind, randomized, controlled study by Markowitz and colleagues compared the efficacy and safety of raltegravir with those of efavirenz in treatment-naïve patients. Patients were randomized to receive raltegravir at 4 doses (100 mg twice daily, 200 mg twice daily, 400 mg twice daily, and 600 mg twice daily) or efavirenz (600 mg once daily); all groups received tenofovir 300 mg/day and lamivudine 300 mg/day. At 48 weeks, total serum cholesterol, LDL cholesterol, and TG levels did not increase in the raltegravir groups, but they were increased in the efavirenz group.
Current Perspectives on HIV-Associated METABOLIC and MORPHOLOGIC Abnormalities

HIV-ASSOCIATED MORPHOLOGIC ABNORMALITIES: AN OVERVIEW

Presented by Julian Falutz, MD

Body Composition Changes
Long-term (5-year follow-up) data on morphologic changes associated with ART are emerging from the FIRST study. A combination of bioelectric impedance analysis (BIA) and anthropometrics was used to evaluate 422 HIV-infected patients who were randomized to 1 of 3 HAART strategies: a PI-based regimen, an NNRTI-based regimen, or a PI-NNRTI combination regimen; all patients received a thymidine nucleoside analogue. The results suggest that regardless of treatment randomization arm, patients experienced a general loss in subcutaneous adipose tissue (SAT) (Figure 4a). There was a concomitant increase of visceral adipose tissue (VAT) over the 5-year period (Figure 4b). The changes observed in SAT and VAT were not significant between treatment arms. Among patients with more advanced HIV who initiate ART, there is what has sometimes been called a “return to health phenomenon,” comprising an increase in fat in the first 6 months after beginning treatment, followed by a decrease in SAT in subsequent months. It is important to recognize that the FIRST study was a “strategy” study, in that it did not merely compare different drug regimens but instead looked at long-term outcomes based on types of drugs used as initial therapy in a real-world setting. Critics of the study note that the results were influenced by frequent switching among the drugs, while supporters of the study point to the same finding—that drug switching is frequent in real-life settings and contributes significantly to long-term outcomes.

Lipodystrophy Overview
Lipodystrophy is the umbrella term for multiple phenotypes of body fat changes that include both lipoatrophy and lipohypertrophy. Lipoatrophy is the term used for fat loss in the face, upper and lower extremities, and buttocks and is related to a loss

[Disclosure: Donald Kotler, MD helped design the metabolic sub-study of the FIRST study and is a coauthor of the publications related to body composition and metabolic alterations.]

Figure 4a. FIRST Study: Changes in Waist SAT in ART-Naive Persons Treated With a PI, NNRTI, or PI + NNRTI Regimen

Figure 4b. FIRST Study: Changes in Waist VAT in ART-Naive Persons Treated With a PI, NNRTI, or PI + NNRTI Regimen

FIRST, Flexible Initial Retrovirus Suppressive Therapies study; ART, antiretroviral therapy; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

of SAT. Lipohypertrophy is the term used for fat accumulation within the abdomen, breasts, and anterior or posterior neck (also called “buffalo hump”). Lipohypertrophy is the term used for fat accumulation within the abdomen, breasts, and anterior or posterior neck (also called “buffalo hump”). This intra-abdominal fat is located in the omental/mesenteric or retroperitoneal compartments, which together are referred to as the visceral compartment. Patients may present with either or both of these alterations in fat compartments. Of note, cross-sectional studies have not linked the various changes in body compartments, so their coexistence could be coincidental, as both abnormalities have been observed frequently. The development of body fat changes is multifactorial, and thus the risk factors for the development of fat loss and fat gain are distinct.

**Lipoatrophy Risk Factors**

In multiple epidemiological studies, risk factors for the development of lipoatrophy include those associated with HIV disease itself (e.g., duration and severity of illness, CD4 cell count nadir), those related to ART, and those that are host related (e.g., increasing age, gender, race). The specific ARVs that have been associated with lipoatrophy are the thymidine analogues, including stavudine and zidovudine. The strongest association is with stavudine and has been widely demonstrated in the literature.\(^{53,54}\)

In recent years, basic scientific research has led to a greater understanding of how chronic inflammation in adipose tissue contributes to the development of lipoatrophy (Figure 5). More has also been learned about the impact of genetic and environmental host factors and concomitant conditions such as obesity, which affect the development and presentation of lipoatrophy. In addition, a preliminary study has identified a possible genetic susceptibility to lipoatrophy related to a polymorphism in the resistin gene.\(^{55}\)

**Lipohypertrophy Risk Factors**

In terms of lipohypertrophy, data from the HOPS cohort suggest that associated risk factors are numerous and seemingly disparate. They include increasing age, hemophilia, undetectable viral load at ≥2 years, increased duration of HAART, race, advanced HIV progression, as well as body mass index (BMI) ≥26 kg/m2.\(^{53}\)

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**Figure 5. Factors Contributing to Lipoatrophy**

![Diagram showing factors contributing to lipoatrophy](image)

- HIV
- Chronic inflammation
- Immune reconstitution
- Comorbidities
- Host
- Genetics
- Environment
- Antiretroviral Therapy
  - tNRTIs
  - NNRTIs?
  - ntNRTIs?
  - PIs?

TNRTIs, thymidine analogue nucleoside reverse transcriptase inhibitors; ntNRTIs, nonthymidine nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors.

Courtesy of Esteban Martinez, MD.
Clinical Significance

Lipoatrophy is significant for 2 main reasons. The first relates to its pathogenesis and how that relates to CV risk. The second concerns its devastating effects on overall patient well-being. A normal function of adipose tissue is to regulate free fatty acid (FFA) concentrations by suppressing the release of FFAs in the circulation and stimulating their increased uptake. However, patients with reduced fat stores, such as those with lipoatrophy, may lose the ability to clear postprandial FFAs, resulting in elevated FFA levels in the circulation. The elevated FFA levels have multiple effects on target organs, including fatty liver, pancreatic β-cell dysfunction, impaired glucose metabolism, and atherosclerosis.56

Julian Falutz: “I think the other message is that lipoatrophy is associated with and is probably a risk factor for insulin resistance, so there are more than just quality-of-life issues, which is not to minimize the importance of those. But there are also potential long-term consequences that need to be factored into our educational efforts.”

Lipoatrophy Evaluation

Studies attempting to assess the presence and extent of lipoatrophy have used a variety of definitions for the condition.3 Facial lipoatrophy is perhaps the best defined, having severity scales that combine photographic images with physical descriptions in order to establish reasonably objective criteria that can be used in determining appropriate management strategies.

Data from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study indicate that subjects who noticed a loss of fat had significant SAT depletion, as measured by whole-body magnetic resonance imaging (MRI) scans, compared with controls. However, even patients who did not notice fat loss also had significantly less fat than controls.57 This result suggests that lipoatrophy and its associated metabolic alterations are more than simply cosmetic phenomena.

While not commonly performed in routine clinical practice, anthropometric measurements have been used to identify differences in the rates of lipoatrophy and lipohypertrophy in HIV-infected men and women. In a study published by Jacobson and colleagues using skin-fold measures, investigators identified 2 distinct syndromes and different risk factors associated with fat atrophy compared with fat deposition. In addition, men had a higher rate of lipoatrophy than women (38% versus 26%, P=.009), and women had a higher rate of lipohypertrophy than men (53% versus 40%, P=.009).58

The metabolic substudy of ACTG 384 used dual energy X-ray absorptiometry (DEXA) to image and measure changes in trunk and limb fat during ART in treatment-naïve individuals (Figure 6). Investigators who studied patterns of trunk and limb fat changes noted that the changes often occurred in the same direction but sometimes were manifest in opposite directions, eg, trunk fat gain and limb fat loss. These findings again point to the likelihood that fat accumulation and loss are distinct phenomena rather than redistribution of fat from one area to another.59

Lipoatrophy Clinical Data

ARV drugs have differential effects on long-term lipoatrophy risk. Of the NRTIs, the data implicating stavudine in the development of lipoatrophy are substantial, consistent, and have resulted in a sharp decline of stavudine use in initial treatment regimens—at least in countries where nonthymidine analogue options are presented by Paul Sax, MD

**Figure 6.** ACTG 384: Changes in Trunk and Limb Fat in Treatment-Naïve Patients

![](chart.png)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Directionally Concordant Changes at Week 64</th>
<th>Directionally Discordant Changes at Week 64</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fat gain in limbs and trunk</td>
<td>Fat gain in trunk, fat loss in limbs</td>
</tr>
<tr>
<td>36%</td>
<td>32%</td>
<td>26%</td>
</tr>
</tbody>
</table>

*Directionally discordant changes measured by DEXA.

**P** <.001 vs % patients who gained fat in the trunk and lost fat in the limbs. Adapted with permission from Lippincott, Williams and Wilkins. http://www.lww.com.


Current Perspectives on HIV-Associated METABOLIC and MORPHOLOGIC Abnormalities
available. Lipoatrophy is seen to a greater extent in regimens containing stavudine plus didanosine, compared with regimens containing abacavir/lamivudine or tenofovir/emtricitabine. In addition, the A5005s metabolic substudy of ACTG 384 found a stronger association between lipoatrophy and the use of stavudine plus didanosine compared with zidovudine plus lamivudine ($P<.05$) (Figure 7). Data from the GS 903 study at 144 weeks demonstrated a greater effect of stavudine plus lamivudine ($n=162$) on lipoatrophy (mean limb fat loss) compared with tenofovir plus lamivudine ($n=170$). After 3 years of therapy, mean total limb fat was 4.5 kg in the stavudine group ($n=117$) versus 8.6 kg for the tenofovir group ($n=115$).

The Abacavir versus d4T plus Efavirenz (ABCDE) study was a prospective, randomized, open trial designed to compare the efficacy and toxicity of abacavir with stavudine in ARV-naïve patients. Patients were randomly assigned to receive abacavir (300 mg twice daily; $n=115$) or stavudine (30 mg twice daily; $n=122$); both groups’ regimens were combined with lamivudine (150 mg twice daily) and efavirenz (600 mg once daily). Fewer patients assigned to abacavir developed clinical signs of lipoatrophy (4.8% versus 38.3%; $P<.001$) than did those assigned to stavudine. DEXA scans performed in 57 patients showed significantly greater total limb fat loss in the stavudine arm ($-1579$ g versus $913$ g; $P<.001$).

Besides stavudine, other studies have identified an association between lipoatrophy and long-term use of zidovudine. In the Community Programs for Clinical Research on AIDS (CPCRA) 061 metabolic substudy, Shlay and colleagues examined the differential effects of NRTI Therapies on Lipoatrophy in the A5005s Substudy of ACTG 384. The Abacavir versus d4T plus Efavirenz (ABCDE) study was a prospective, randomized, open trial designed to compare the efficacy and toxicity of abacavir with stavudine in ARV-naïve patients. Patients were randomly assigned to receive abacavir (300 mg twice daily; $n=115$) or stavudine (30 mg twice daily; $n=122$); both groups’ regimens were combined with lamivudine (150 mg twice daily) and efavirenz (600 mg once daily). Fewer patients assigned to abacavir developed clinical signs of lipoatrophy (4.8% versus 38.3%; $P<.001$) than did those assigned to stavudine. DEXA scans performed in 57 patients showed significantly greater total limb fat loss in the stavudine arm ($-1579$ g versus $913$ g; $P<.001$).

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Figure 7. Differential Effects of NRTI Therapies on Lipoatrophy in the A5005s Substudy of ACTG 384

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Median % change in limb fat from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-20%</td>
</tr>
<tr>
<td>16</td>
<td>-10%</td>
</tr>
<tr>
<td>32</td>
<td>-30%</td>
</tr>
<tr>
<td>48</td>
<td>-40%</td>
</tr>
<tr>
<td>64</td>
<td>-50%</td>
</tr>
<tr>
<td>80</td>
<td>-60%</td>
</tr>
</tbody>
</table>

$P<.05$ intragroup.

$P<.05$ intergroup.

NRTI, nucleoside reverse transcriptase inhibitor; ACTG, AIDS Clinical Trials Group; ZDV+3TC, zidovudine plus lamivudine; ddl+d4T, didanosine plus stavudine.


In the MEDIKLAS study, van Vonderen and colleagues prospectively evaluated the role of zidovudine/lamivudine versus nevirapine in glucose metabolism and body composition in HIV patients. Patients were randomized to receive zidovudine/lamivudine and lopinavir/ritonavir (400 mg/100 mg bid) or nevirapine and lopinavir/ritonavir (533 mg/133 mg bid). At 24 months, the zidovudine/lamivudine group experienced a loss in limb fat from baseline ($P<.05$), whereas the nevirapine group experienced a net limb fat gain. In the GS 934 study, data at week 144 showed that treatment-naïve patients in the emtricitabine plus tenofovir efavirenz regimen had significantly more median limb fat (8.3 kg versus 7.4 kg at baseline) than did the zidovudine/lamivudine plus efavirenz group, which, in fact, experienced significant limb fat loss (4.9 kg versus 6.0 kg at baseline) ($P<.001$).

ACTG 5142 was a randomized, prospective, open-label study looking at the effects of class-sparing strategies. It compared 3 regimens: a PI plus a NNRTI (lopinavir/ritonavir plus efavirenz); a PI (lopinavir/ritonavir) plus 2 nucleosides; and a NNRTI (efavirenz) plus 2 nucleosides in ARV-naïve patients. Nucleosides included lamivudine combined with either zidovudine, extended-release stavudine, or tenofovir. Somewhat surprisingly, lipoatrophy (defined as ≥20% decline in limb fat) was greatest in the efavirenz plus nucleoside arm and lowest in the nucleoside-sparing arm. In terms of nucleoside effects, the lowest percentage of patients with lipoatrophy was in the tenofovir-treated group and the highest was in the stavudine-treated group, with zidovudine falling in the midrange.

Although these were not randomized comparisons, these data are nonetheless encouraging with respect to the potential benefits of thymidine-sparing strategies for initial nucleoside therapy. Even though the effect of efavirenz in this study is somewhat puzzling, the results point to the importance of the ARV regimen as a whole, and the combined effects ARV drugs have on the metabolic and morphologic condition of HIV patients in particular. It is difficult to compare the studies mentioned above with ACTG 5142 because different definitions of lipoatrophy were utilized and the results expressed as a proportion of subjects reaching the specified end point rather than as a median or mean change.

**Lipoatrophy Switch Treatment Strategies**

Since lipoatrophy was recognized as an adverse event among HIV-infected patients, clinicians have been exploring treatment strategies that will either reverse or prevent fat loss in those patients receiving ART. The NEFA study evaluated a PI-sparing switch strategy that replaced PIs with either nevirapine,
Based on patient and clinician assessments of lipoatrophy, the NEFA study results did not demonstrate any significant improvement in fat loss at 12 months following PI withdrawal, although in the abacavir arm, the proportion of patients with fasting lipid levels requiring therapeutic intervention decreased significantly. However, there was also a trend toward a higher virologic failure rate in the abacavir arm compared with either the nevirapine or the efavirenz arm; hence, this strategy cannot be recommended.

Patterns of gradually increasing body fat have been observed in a number of nucleoside switch studies. In the Trial to Assess the Regression of Hyperlactatemia and to Evaluate the Established Regression of Lipodystrophy (TARHEEL), patients were switched from stavudine to either abacavir or zidovudine. Both abacavir and zidovudine did confer improvements in limb and trunk fat at 48 weeks, along with increases in mitochondrial DNA (mtDNA) content in peripheral blood mononuclear cells (PBMCs). However, mtDNA levels remained substantially lower than in the HIV-negative population. Today, however, switching to zidovudine is not a strategy likely to be pursued, given concerns about its potential to induce lipoatrophy.

Additional studies have demonstrated that upon switching to thymidine analogue-sparing regimens, patients may in fact achieve gains in limb fat. In ACTG A5125, patients were randomized to switch their ARV regimen to either open-label lopinavir/ritonavir (533 mg/133 mg twice daily) plus efavirenz (600 mg once daily), or efavirenz plus 2 NRTIs. At week 48, the lopinavir/ritonavir plus efavirenz group experienced a nonsignificant increase in limb fat (median +.56 kg) versus the NRTI-containing arm’s limb fat loss (–.25 kg) (P=.097). The RAVE study was a randomized, open-label, comparative study of a switch from either zidovudine or stavudine to either tenofovir (n=52) or abacavir (n=53) regimens. At 48 weeks, a significant and similar increase in limb fat took place in the tenofovir (+.33 kg; P=.01) and abacavir (+.48 kg; P=.001) groups. In the Mitochondrial Toxicity (MITOX) study, HIV patients were randomized to either switch from a thymidine analogue regimen (zidovudine or stavudine) to abacavir and continue all other ART (n=42) or continue taking their current thymidine analogue regimen (n=43). At 104 weeks, the abacavir group experienced a mean increase in limb fat of 1.26 ± 2.02 kg (35%; P=.001) while the zidovudine and stavudine group experienced a mean increase of 0.49 ± 1.38 kg (13%; P=.039). Lastly, in the GS 903E study, data at 288 weeks showed that after patients switched from stavudine to tenofovir, median limb fat increased from 3.8 kg to 4.8 kg (P<.0001). However, the magnitude of increase totaled about 25% of the estimated loss. The gain is often barely clinically detectable. It is uncertain whether there will be a further, time-dependent increase in SAT content in these patients.

**Adjunct Therapies**

In addition to making changes in ARV regimens to prevent or treat lipoatrophy, clinicians have evaluated the efficacy of other adjunct drugs as treatments for fat loss. However, the FDA has not yet approved any drug for this indication. While there was initially hope that rosiglitazone might play a role as a treatment for lipoatrophy, clinical trial data have generally been disappointing. Although positive results on lipoatrophy, insulin sensitivity, and metabolic indices were reported in one trial, in 3 other studies, no improvements in limb fat were noted, and treatment was sometimes associated with increased TG and cholesterol levels. There have, however, been some positive data for another thiazolidinedione, pioglitazone, including quantifiable improvements in limb lipoatrophy in those patients who were not also receiving stavudine. Pioglitazone also does not appear to have adverse effects on lipid levels. Even so, the use of the glitazone class of drugs solely to treat lipoatrophy in HIV patients should be avoided, given recent concerns raised about their potential negative impact on CV risk. Because studies have indicated that metformin may contribute to additional fat loss in patients with lipoatrophy, it also should not be used in these patients, although it may be useful in patients with lipohypertrophy.

The experimental agent uridine has been shown to significantly increase limb and total body fat compared with placebo in patients still taking stavudine. However, the therapy also promotes an increase in intra-abdominal or truncal fat. Lastly, testosterone replacement therapy results in reduction of all fat stores and should not be used as a treatment for lipoatrophy.
ART-RELATED COMPLICATIONS IN HIV PATIENTS: FOCUS ON LIPOHYPERTROPHY

Presented by Graeme Moyle, MD

Data from a number of cohort studies have indicated that both lipoatrophy and lipohypertrophy (the morphologic changes sometimes called lipodystrophy) occur in all patient populations, including those not infected with HIV. However, the prevalence of both forms of fat changes is higher in HIV-infected patients treated with ART. Mallon and colleagues, as well as others, have demonstrated that initiating ART results in an initial gain in overall weight, with both central and limb fat and lean mass increases, suggestive of restoration to health. However, in studies where patients' ARV regimens include thymidine nucleosides, the initial return to health is followed by maintenance of central fat and loss of limb fat. This effect is not restricted to thymidine analogue therapy, however. For example, in the 5005s substudy of ACTG 384, patients treated with efavirenz (n=31) gained limb fat (1.8%, as measured by DEXA) compared with those treated with nelfinavir (n=33), who lost 13.1%, and those receiving didanosine plus stavudine experienced more rapid fat loss than those on zidovudine plus lamivudine. The FRAM study has also clearly described the existence of 2 independent morphologic events that may or may not occur in the same individual; that is, researchers found no clear link between the presence of peripheral lipoatrophy and central lipohypertrophy.

The Metabolic Syndrome

The metabolic syndrome represents a constellation of CVD and diabetes mellitus type 2 risk factors that are related primarily to insulin resistance or truncal obesity. The metabolic syndrome is a valuable concept for clinicians, in that it helps to identify those individuals at highest risk for CVD and diabetes. A number of definitions have been proposed over the years, most of which can be summarized in terms of increased abdominal fat, some measure of insulin resistance, hypertension, and dyslipidemia. Defining lipohypertrophy in persons with HIV is difficult because one must rule out all the other risk factors and identify whether increased VAT and other changes are being driven by HIV or by these other factors.

Insulin Resistance

In the setting of HIV infection, a number of influences may contribute to the development of insulin resistance. They include the classic risk factors that apply to the general population (eg, abdominal obesity, physical inactivity, genetic predisposition, older age, and dyslipidemia), as well as factors that are of particular relevance in HIV (eg, lipoatrophy, reduced adiponectin levels, increased fat in the liver and muscles, inflammation, low testosterone levels, oxidative stress, hepatitis C coinfection, and medication effects).

The question of whether the metabolic syndrome is more common among individuals with HIV infection per se has been examined in a number of cohort studies. Hadigan and colleagues performed a case-control study using control subjects from the Framingham offspring cohort. They found that HIV patients with lipodystrophy had higher rates of impaired glucose tolerance, hypercholesterolemia, and hypertriglyceridemia than did controls. An evaluation of the Multicenter AIDS Cohort Study (MACS) 1999-2004 cohort found more metabolic syndrome overall among HIV-infected men compared with HIV-negative men—particularly in association with elevated TGs, elevated fasting glucose (>110 mg/dL), and reduced HDL levels. More recent data derived from MACS confirmed that cumulative exposure to NRTI therapy was associated with slight decreases in body circumference measurements, whereas HIV infection was associated with increases in waist circumference independent of ART exposure. Data from the HIV Epidemiology Research Study (HERS) have also confirmed an increased likelihood of metabolic syndrome in HIV-infected women compared with non–HIV-infected controls.

Short-term studies in healthy volunteers indicate that ritonavir, indinavir, lopinavir/ritonavir, and stavudine are associated with insulin resistance. However, in HIV patients, no insulin resistance was observed with emtricitabine/tenofovir plus either atazanavir/ritonavir or saquinavir; nor was it observed with either tenofovir/lamivudine combined with lopinavir/ritonavir or fosamprenavir/ritonavir. The D:A:D study looked at the risk of developing diabetes among patients on ART and found that diabetes risk was driven by cumulative exposure to nucleoside drugs, with stavudine, zidovudine, and didanosine being significantly associated with diabetes. Additional data from the cross-sectional study at the Infectious Disease Unit of the Hospital del Mar, Barcelona, Spain, demonstrated that stavudine and lopinavir were the individual drugs most strongly associated with the metabolic syndrome over a 1-year period. The study also showed that the risk of the metabolic syndrome is associated with greater PI exposure.

Understanding the metabolic syndrome and how it relates to HIV infection is important because the metabolic changes associated with the syndrome contribute to an increased risk of CVD events. Identifying HIV patients with the metabolic syndrome thus identifies people at greater risk of CV events. The results of the D:A:D study suggest that it is the individual metabolic changes that make up the metabolic syndrome which increase the risk of CVD, not necessarily the metabolic syndrome itself.
Lipohypertrophy Evaluation
As mentioned earlier, lipohypertrophy manifests in HIV patients as fat accumulation in the abdomen, breasts, anterior or posterior neck (also called “buffalo hump”), and, less commonly, other areas. Measuring body composition makeup (ie, lean body mass versus fat and bone) does not provide adequate assessment, and specific challenges exist when assessing accumulations beyond the abdomen.

To evaluate lipohypertrophy, the clinician assesses the patient’s self-report (a subjective measure of lipohypertrophy) and supplements the results by physical examination, which could include anthropometric measurements such as skin folds, waist circumference, and waist-to-hip ratio. BMI is not a useful tool for the estimation of fat distribution. Several imaging modalities are available for a more in-depth look at lipohypertrophy; they include DEXA, ultrasound, computed tomography (CT), and MRI. DEXA, which produces a detailed image of body components, cannot detect whether truncal fat is subcutaneous or visceral; however, it is the gold standard for assessing limb fat and has a margin of error of only 1% to 5%. DEXA also has the advantage of being rapid, patient-friendly, and using low doses of radiation (compared with CT scanning). However, the downsides are the estimation of fat distribution. Several imaging modalities are available for a more in-depth look at lipohypertrophy; they include DEXA, ultrasound, computed tomography (CT), and MRI. DEXA also has the advantage of being rapid, patient-friendly, and using low doses of radiation (compared with CT scanning). However, the downsides are relatively high cost, lack of consensus values and categorical cutoffs, and lack of reimbursement by third-party payers in the United States. In clinical trials, CT and MRI are the most widely used scans for assessing visceral fat accumulation but are not practical for the office.

Office Tip: Assessing VAT
An increase in VAT can be easily assessed by measuring waist circumference. In addition to measuring weight changes on the typical office scale, a measuring tape is a useful tool. An increase in waist circumference is a risk factor for increasing CV mortality as well as other CV events. Further, studies of HIV-negative patients have shown that as VAT increases, all-cause mortality increases as well.

Lipohypertrophy Interventions
The fundamental tools for managing fat accumulation and the metabolic syndrome are diet, exercise, pharmacological interventions that improve insulin sensitivity or insulin production, cosmetic surgery, and modification of HAART. As with lipodystrophy, no FDA-approved therapy is available for this indication.

A study by Fitch and colleagues looked at the effectiveness of lifestyle interventions for the management of the metabolic syndrome in HIV-infected individuals. Patients who received lifestyle modification (ie, dietary counseling once weekly and 3 hours of physical activity per week) exhibited mild to moderate benefits similar to those reported in studies of non–HIV-infected patients with the metabolic syndrome; these included improvements in systolic blood pressure, improvements in waist circumference, and small improvements in glycosylated hemoglobin A1c (HbA1c) and lipodystrophy scores (Figure 8). In a similar study, patients were either given (n=42) or not given (n=38) dietary intervention at the initiation of HAART. The group given the intervention reduced their caloric intake and prevented increases in BMI or waist-to-hip ratio. The patients who received this intervention had a lower incidence of developing dyslipidemia (17%) compared with controls (50%, P<.05), who did not receive the intervention.

Several studies have demonstrated a benefit from using metformin in the treatment of lipohypertrophy, especially when combined with exercise, in patients who have markers of insulin resistance (eg, elevated fasting insulin or 2-hour glucose level). In the first of these, Hadigan and colleagues conducted a small randomized, double-blind, placebo-controlled pilot study to investigate the safety and efficacy of metformin therapy in HIV patients. Patients were randomized to receive metformin (500 mg twice daily; n=14) or placebo (n=12) for 3 months. The researchers found that compared with the placebo group, patients taking metformin experienced significant weight reduction (–1.3 kg versus 1.1 kg; P=.005), a significant decrease in waist circumference (–1.1 cm versus 1.1 cm; P=.02), a decrease in VAT (–1115 mm² versus 1191 mm²; P=.08), as well as a significant improvement in insulin sensitivity, as measured by mean insulin AUC following oral glucose tolerance testing (–2930 μIU/mL versus –414 μIU/mL; P=.01).

Driscoll and colleagues conducted a prospective, randomized trial to investigate whether metformin in combination with exercise, compared with metformin alone, improves CV risk indices in patients with HIV. Patients were randomized to receive 1 of 2 regimens for 3 months: metformin alone (500 mg twice daily) with a dose increase to 850 mg twice daily after 2 weeks and lipodystrophy scores (Figure 8).

Figure 8. Benefits of Exercise and Dietary Changes in HIV Patients With the Metabolic Syndrome

(n=18) or metformin plus exercise 3 times weekly (n=19). The researchers found that patients who received metformin plus exercise experienced a significant decrease in median waist-to-hip ratio (–0.02 versus –0.01; *P*=.026) compared with the metformin monotherapy group. However, metformin has been shown to lead to weight loss in the periphery and can contribute to increased lipoatrophy.

The use of steroids and hormones may also have mixed effects on the patient with lipohypertrophy. For instance, one study with oxandrolone demonstrated a favorable impact on abdominal VAT but also reported peripheral fat loss and unfavorable effects on lipid levels (eg, increased LDL and decreased HDL cholesterol). Similarly, testosterone supplementation has been shown to reduce visceral or trunk fat while simultaneously reducing fat in the extremities (Figure 9). Such therapies may be useful for patients who have the metabolic syndrome only, with little or no obvious lipoatrophy; however, these treatments could have the effect of unmasking or aggravating lipoatrophy.

Growth hormone has also been studied as a treatment for lipodystrophy, based on data indicating that growth hormone production is lower in people with lipoatrophy than in the general population and that its secretion is inversely related to VAT. Investigators looked at the effect of recombinant human growth hormone (rhGH) treatment in patients with increased waist circumference and waist-to-hip ratio. A significant reduction in VAT was seen after 12 weeks among patients treated with rhGH compared with placebo. The studies also showed positive effects on lipid levels. Prolonged therapy with lower doses of the drug led to some maintenance of the effect. However, subjects lost much of the benefit once the drug was withdrawn.

The other adjunct therapy of interest is tesamorelin (TH9507). Tesamorelin is itself a hormone, which stimulates the production of growth hormone. An initial Phase III study compared subcutaneous injection of either tesamorelin 2 mg or placebo. There was a marked improvement in VAT among patients treated with tesamorelin compared with placebo (–15.2% versus +5.0%, respectively, *P*<.001) (Figure 10). Investigators noted that the greater the amount of VAT, the greater the reduction in VAT from baseline, suggesting that the drug is a relatively targeted treatment for increased VAT. However, as was seen with rhGH, the treatment benefit was largely lost within 24 weeks of drug cessation.

**Figure 10.** TH9507 versus Placebo: Mean Change in VAT and SAT at Week 26

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change (%)</th>
<th>VAT</th>
<th>SAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH9507 (n=275)</td>
<td>-15.2%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0%</td>
<td>0.4%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo (n=137)</td>
<td>5.0%</td>
<td>0.4%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

<sup>a</sup>*P* <.001 vs placebo.  <sup>b</sup>*P* <.001 vs placebo.  <sup>c</sup>Assessed by abdominal CT scan.  <sup>d</sup>Assessed by DEXA scan.

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

**Figure 9.** ACTG 5079: Median Changes in Fat as Assessed by DEXA Scan

<table>
<thead>
<tr>
<th>Fat Type</th>
<th>Change from Baseline at Week 24 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>4.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.8%</td>
</tr>
<tr>
<td>Trunk Fat</td>
<td>-9.9%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Extremity Fat</td>
<td>-10.1%&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup>*P* <.001 vs placebo.

Lipodystrophy-Associated Psychological Disturbances: Increasing Awareness and Management

Presented by Michael Stein, MD

The metabolic and morphologic complications associated with HIV, and their treatment, have ramifications beyond their physiological effects. In fact, for many patients, the psychosocial implications of the lipodystrophy syndromes can overshadow the clinical implications of redistribution of adipose tissue. Alleviating the psychosocial effects of lipodystrophy may be particularly challenging, given the substantially higher rates of psychiatric disorders (including major depression and generalized anxiety disorder) among patients with HIV (Table 4). Data from the HIV Cost and Services Utilization Study (HCSUS) point to very high rates of major depression, generalized anxiety disorder, and panic attacks among those infected with HIV compared with the general population. In addition to psychiatric diagnoses, individuals with HIV infection have high rates of substance abuse, including drug dependence (12.5%) and heavy drinking (18.5%).

Body Image Perception Among HIV Patients

The psychosocial implications of the lipodystrophy syndrome are quite profound and reflect the importance that physical appearance has to our perception of health and illness. Lipodystrophy and facial disfigurement in particular are signs associated with illness and old age. Qualitative studies performed in recent years have uncovered that the disfigurement associated with lipodystrophy has become a signifier of HIV status; some are calling it the “new Kaposi’s sarcoma” because it is believed to lead to unwanted disclosure of disease status and to stigma. Although there may not be significant awareness of lipodystrophy in the general population, it is particularly stigmatizing within the populations at risk.

Lipodystrophy-related disfigurement can lead to loss of confidence and self-esteem and to diminished feelings of attractiveness, which can negatively impact a patient’s sexual life. In addition, lipodystrophy syndrome can adversely affect social functioning and employment. Despite the potent psychosocial effects associated with lipodystrophy, controlled studies have found that it is not associated with how HIV-infected people view their general health. Possible effects of prominent lipodystrophy on the patient include stigmatization, anxiety and depression, and a reduction in medication adherence.

Given continued aging of the HIV patient population, these issues should be viewed from the perspective of this older population. Sharma and colleagues recently published a study looking at the factors associated with a negative body image among 550 older men (mean age 55 years) with or at risk for HIV infection. The sample included 322 HIV-infected subjects and 228 people at risk and comprised 55% African Americans, 62% current or former injection drug users, and 69% heterosexuals. Thirty-one percent of the subjects reported what would be considered a negative body image. According to multivariate analysis, factors that were associated with a negative body image included higher BMI, higher CES-D (a depression scale) ratings, fair or poor health, and erectile dysfunction. HIV status itself did not seem to affect body image, but in the group of HIV-positive patients, factors associated with negative body image included higher BMI, poor health, and peripheral weight loss. In this study, neither HIV status nor lipodystrophy syndrome was associated with erectile dysfunction.

The same research group previously evaluated factors associated with negative body image among 225 HIV-infected and 207 uninfected women. Subjects participated in standardized interviews during which investigators obtained height and weight measurements and sociodemographic data and elicited agreement with the statement: “Overall I am satisfied with my body shape.” They reported that 39% of the women were obese and 47% had a negative body image. In this study, factors that were independently associated with negative body image included HIV infection, higher BMI, and depression.
Lipodystrophy and Depressive Symptoms

The relationship between lipodystrophy and symptoms of depression is potentially bidirectional. The morphologic changes (facial lipoatrophy in particular) associated with looking ill and/or older than one’s age may give rise to depressive symptoms and social withdrawal. At the same time, individuals who are depressed may have a poorer body image and perceived appearance and consequently judge their lipodystrophy to be particularly severe.

However, most cross-sectional studies have not found an association between depression and lipodystrophy. Data from the MACS cohort, for example, which compared HIV-infected patients with HIV-negative controls, do not indicate an increase in depression over and above having an HIV diagnosis.\(^\text{113}\) It is also important to consider that depressive disorders are common among HIV-infected individuals (ranging between 20% and 60%), irrespective of the presence of lipodystrophy.\(^\text{109,114}\) Although lipodystrophy syndrome and depression may present simultaneously, the relationship between them is not clear.

One of the difficulties in establishing an association between lipodystrophy and depression is the complexity of measuring both phenomena. In addition to the lack of clear definitions for both lipoatrophy and lipohypertrophy, typical quality-of-life and mood measures are not designed to be sensitive or specific enough to accurately gauge the potential psychological consequences of lipodystrophy in individual patients. However, some specific psychometrically valid tools have been designed to distinguish between the social and psychological impact of body image changes associated with lipodystrophy.\(^\text{115,116}\) These instruments use more targeted questions, which attempt to elicit patients’ feelings about their bodies, such as, “Do you feel embarrassed by your body?” or, “Do you avoid situations where others can see your body?” Some of the questionnaires are quite long and ask about specific body parts and how changes in those body parts affect the patient’s self-perception.

Data from Crane and colleagues suggest that the more severe the lipodystrophy, the greater its impact on mean depression scores and health-related quality of life (HRQoL) indices.\(^\text{110}\) This cross-sectional study enrolled 311 patients from the University of Washington Cohort in which patients completed depression (PHQ-p), HRQoL (EQ-5D), adherence, drug and alcohol use, and body morphology (FRAM) assessments. In particular, using a scale ranging from none to mild, to moderate lipoatrophy, mean depression scores were highest among patients with moderate lipoatrophy and lowest among those without morphologic abnormalities. Similarly, the lowest mean HRQoL scores occurred in those patients with moderate lipoatrophy or lipohypertrophy, whereas the highest scores were reported in patients without any such abnormalities. Although it is not surprising that more severe body changes should have more impact on depression scores, it is interesting to note that moderate lipoatrophy has been associated with a higher mean depression score than moderate lipohypertrophy.\(^\text{110}\)

A widely discussed study performed in the late 1990s that looked at the attitudes toward lipodystrophy among 75 primarily homosexual men with relatively advanced HIV disease illustrates the significance of these issues for patients. Patients were given several options and asked how many years of their life they would give up to live in good health without lipodystrophy—in effect, they were asked whether they would trade years alive for a better quality of life. Given a case scenario consisting of sample photographs of severe lipodystrophy syndrome, 67% responded that they would give up at least 1 year of life to avoid living with lipodystrophy, and 73% reported that they would be willing to incur at least a 1% additional risk of death to avoid having lipodystrophy.\(^\text{117}\)

Lipodystrophy and Sexual Functioning

In controlled studies, lipodystrophy has not been associated with changes in levels of testosterone, sex hormone–binding globulin, prolactin, or cortisol. However, in uncontrolled research, lipodystrophy has been associated with decreased libido in homosexual men, which may have to do with its detrimental effect on feelings of attractiveness.\(^\text{118}\) These studies did not control for other factors that can have an impact on libido, such as depression or antidepressant medication utilization; thus, the validity of this association is uncertain.

Lipodystrophy and Treatment Adherence

A significant concern among clinicians is whether lipodystrophy has an effect on treatment adherence. Data from several studies have identified a significant association between body fat changes and reduced treatment adherence.\(^\text{119-121}\) In one study, which evaluated 358 patients via a self-administered questionnaire, 22% reported treatment nonadherence. A univariate analysis found that abnormal fat distribution was significantly associated with treatment nonadherence, although this association was not significant in the multivariate analysis.\(^\text{119}\) In another large study (N=277), which did adjust for multiple related factors, the number of self-reported lipodystrophy symptoms was independently associated with reduced treatment adherence.\(^\text{120}\) Furthermore, a recent study by Crane and colleagues demonstrated that even mild lipoatrophy is associated with poorer treatment adherence.\(^\text{118}\) Those observations reinforce the critical importance of lipoatrophy: both mild and moderate lipoatrophy were associated with poorer treatment adherence than that of patients who did not have any morphologic abnormalities.\(^\text{110}\) Additionally, several longitudinal studies have reported that patient-perceived lipodystrophy predicts treatment nonadherence to some degree.
Facial lipoatrophy includes more than the loss of SAT from the cheeks; in severe cases, it can involve the loss of fat from the temporal region as well. Another condition that gets far less attention in the literature is inflammation of the parotid glands, which causes disfigurement to the jawline. It is not clear whether this condition is related to the metabolic syndrome or to HIV infection itself. This symptom is being treated with low-level radiation therapy, which is highly effective and whose side effects seem to be relatively minor. Another key concern at present for many patients with HIV is lipoatrophy of the buttocks, which, in addition to the cosmetic effects, has practical implications, for instance, in terms of how comfortable one can be sitting at one’s desk for a few hours.

The effects of lipoatrophy are experienced differently by men and women. For those men who are interested in looking fit, some SAT loss in the extremities may not be perceived as a bad thing, since it results in a leaner appearance. For women, however, it is a more significant concern because it can lead to a rather vascular look that they perceive as manly. For those who experience fat accumulation in the abdominal area, fat loss in the extremities may make their stomach appear to protrude even more than if they had no lipoatrophy.

Implications of Lipodystrophy From a Patient Perspective

Lipodystrophy remains a problem for highly treatment-experienced patients but also extends beyond this group to treatment-naïve patients. A major roadblock for patients who have not yet begun HAART is the fear of disfigurement as a result of lipodystrophy. Because of this fear, some patients will delay the initiation of therapy until their CD4 cell counts drop to <200 cells/mm³. Among longer-term survivors, who have experienced the life-saving benefits of HAART, lipodystrophy is less likely to discourage them from continuing therapy.

Survey Results: Impact of Lipodystrophy on Patients’ Self-esteem and Quality of Life

The development of an online community of HIV patients (PozHealth@yahoogroups.com) and of nonprofit websites such as facialwasting.org have made possible an informal survey of highly empowered, treatment-experienced patients who share concerns about body-related effects of their HIV therapy. It should be noted, however, that the survey has limitations and should be interpreted with caution, owing to its comprising a biased sample of highly capable, long-term survivors who might have reached out because of more body-related problems. Also, few women and people of color responded to the survey. The patients responding to the survey (N=660, as of November 2007) were overwhelmingly male (87%), white (79%), and 40 years or older (85%). More than 76% have been HIV positive for 10 years or longer, and 63% report having taken HIV medications for 10 years or longer, with most currently taking HAART. Thus, these patients are likely to have been exposed to the drugs that are most strongly associated with lipodystrophy. Ninety percent of respondents reported body changes related to their HIV infection or treatment.

In terms of the types of body changes they have experienced, the most common complaint is facial wasting (75%), followed by buttock wasting (71%), veiny arms or legs (68%), and abdominal fat gain (64%) (Figure 11). In addition, 22% and 17% of respondents, respectively, reported developing a buffalo hump and parotid gland enlargement, and 23% reported increased breast size. When asked about the impact of morphologic changes on their quality of life and self-esteem, 86% of respondents reported experiencing depression or anxiety as a result of their body changes, with 22% acknowledging that they have contemplated suicide as a result of their body changes.

Forty percent of the respondents reported that they have considered stopping their medications or have actually done so because they fear worsening morphologic changes. Looking at specific behaviors that have been affected by their condition, 73% reported reduced sexual activity, 64% have stopped socializing and going out to meet people, and 50% have stopped dating.

Almost 75% of the respondents have used exercise and diet to try to reverse the body changes. Forty-two percent have received facial injections to treat facial wasting, and in an effort specifically to improve body composition, 47% have taken testosterone while 48% have taken dietary supplements (Figure 12). For all the treatments they have tried, 62% report that they have paid out of their own pocket, with just 18% stating that insurance has covered their treatments. In addition, many respondents have made changes to their ARV regimens, 33% switching from stavudine to tenofovir or abacavir or to combination drugs containing tenofovir or abacavir. Another 12% switched from zidovudine to tenofovir or abacavir or to combination drugs containing tenofovir or abacavir.
An evaluation of the most commonly reported topics cited during the past 9 years, both during lectures and on the largest Internet Listserv™, provides a snapshot of patient perceptions and concerns about developing lipodystrophy. Among the most significant is the sense that facial wasting is a marker for HIV infection—similar to what Kaposi’s sarcoma and wasting syndrome used to be—resulting in the unintentional disclosure of HIV status, at least in communities familiar with HIV and its treatment. Patients also report that as their bodies change, they begin to avoid looking at themselves in the mirror and perceive themselves to be aging faster than they should. This dissatisfaction with their appearance can also lead to social isolation and to an avoidance of dating and other situations where they might feel less attractive than they used to be. For people who work in the entertainment industry or service-related fields that place a particular emphasis on appearance, changes in body shape can be especially disturbing. Treatment-experienced patients, whose fears of lipodystrophy at one time may have led them to discon-
continue treatment, are now more likely to look to switch strategies that could prevent or reverse the development of lipodystrophy. Finally, the current surgical and cosmetic treatments for lipoatrophy are expensive, frequently not covered by insurance, and have minimal data proving their long-term effectiveness or safety.

Surgical and Therapy Issues From a Patient Perspective

In general, a significant amount of patient and provider confusion surrounds the surgical treatment options for facial reconstruction, which include those that are FDA-approved, off-label, or available only outside of the United States. Patient education programs on current efficacy and safety are lacking, as is information on durability, cost, and patient assistance programs, even for those surgical treatments that are approved by the FDA. Another key difficulty is that very few insurance companies or health maintenance organizations (HMOs) are covering the cost of these treatments. Thus, the research community needs to help advocate for reimbursement of HIV-related facial reconstruction procedures. As of November 2007, most third-party payers regard these therapies as purely cosmetic in nature, with no regard for the fact that lipoatrophy is a clinical, disease-specific problem with strong risk-factor predictors.

The use of liposuction for the treatment of so-called buffalo hump or neck or breast enlargement is common; however, VAT cannot be reached safely with this method. Like facial lipoatrophy options, liposuction tends to be perceived as cosmetic only and is rarely reimbursed, although there are clinically relevant reasons to link fat accumulation with neck/abdominal pain or sleep apnea diagnosis. Because some studies have suggested that lipohypertrophy may not be an HIV-related condition, justifying reimbursement can be challenging. Another challenge in this field is the lack of a directory of providers who are well experienced in the use of lipoatrophy reconstruction or liposuction procedures. Nonprofit groups such as the Program for Wellness Restoration (PoWeR) are now attempting to collect these data for wide community distribution.

Given the lack of clear information and guidance, many patients are taking matters into their own hands by searching for “natural” or over-the-counter solutions (eg, NucleomaxX [nucleoside extracts from sugar cane] for lipoatrophy, fat burners for lipohypertrophy), special diets, or exercise routines that will help mitigate the body changes they are experiencing. There is a need for solid data on the use of diets lower in simple carbohydrates and of simple exercise regimens easy to adhere to for the management of increased VAT. With the FDA’s recent denial of the approval of Serostim (somatropin [rDNA origin] for injection) for treating VAT accumulation, another concern is that the size of the market for such treatments and their low reimbursement rates may not justify the cost of developing and marketing them.

Several important issues remain: first, how can we best address the needs of 2 HIV patient populations: long-term survivors, who have been exposed to many of the drugs associated with lipodystrophy, and patients just starting treatment, who have concerns about how to prevent those complications? Second, the widespread use of the thymidine analogues in developing countries is likely to result in the development of lipoatrophy and metabolic complications in millions of people around the world. There is a need to advocate for more affordable access in these countries to drugs associated with lower risk of lipodystrophy.
Cosmetic Treatment Options for Facial Lipoatrophy

Facial lipoatrophy is the most common type of fat loss and is often devastating to patients. There are 3 different treatment options that have shown promise in the treatment of facial lipoatrophy: surgery, temporary injectable fillers, and permanent injectable fillers. However, before recommending an appropriate treatment option, the clinician should evaluate the patient to assess facial lipoatrophy severity. The Carruthers Facial Lipoatrophy Severity Rating Scale is one method for assessing the severity of facial lipoatrophy. It uses a photographic scale that stratifies facial lipoatrophy into 4 stages that represent progressively more severe fat loss (Figure 13).¹²² The scale has been vigorously validated so that experts can assign ratings that are statistically consistent.

Surgical Options

Although a traditional face-lift can be effective in the facial lipoatrophy patient, it does not address the underlying problem, which is the loss of SAT volume. As a result, the face will not maintain any improvements that result from the surgery. In addition, the utility of face-lifts is limited by surgical risk and recovery time.

Temporary Injectable Fillers

The most commonly used treatments of HIV-related facial lipoatrophy include both nonpermanent and permanent injections (Table 5). Much of the medical literature on HIV facial lipoatrophy in recent years has focused on the use of injectable poly-L-lactic acid (PLA) (or Sculptra®, which received FDA approval in 2004). The results of the open-label Correction of Facial Lipoatrophy in HIV-Infected Patients (VEGA) study revealed a significant increase in the total cutaneous thickness (TCT), as measured by ultrasound, following the injection of PLA.¹²⁵ In that study, patients received 4 sets of injections beginning at day 0 and repeated this regimen every 2 weeks for a period of 6 weeks. Patients were evaluated by clinical examination, facial ultrasound, and photography at baseline screening and at weeks 6, 24, 48, 72, and 96. Following treatment at week 96, the median TCT had increased significantly, to 6.8 mm (range 3.9-10.1 mm) from baseline (P<.001). In addition, the proportion of patients with TCT >10 mm reached 43% at 96 weeks, after peaking at 61% at week...
Unfortunately, a 10-mm increase in skin thickness does not necessarily correlate with an optimal cosmetic outcome. As a result, patients frequently achieve only partial improvement and are required to continue the treatment, often at a great expense. A study presented at the 14th Conference on Retroviruses and Opportunistic Infections (CROI 2007) looked at patients who had received PLA for facial lipoatrophy. Researchers used CT scans to measure how much actual change in facial volume occurred following 4 treatments. The investigators found that at week 24, in adults with facial lipoatrophy, 4 PLA treatments significantly improved both patient and physician assessments, as well as several quality-of-life domains. However, the treatment did not significantly increase facial soft-tissue volume; rather, it only modestly improved soft-tissue thickness around the injection plane. Although the use of PLA does prevent further deterioration in facial lipoatrophy, it often does not provide optimal correction of the fat loss. Therefore, it is most effective in those patients with stage 1 lipoatrophy.

A concern with the use of PLA injection is the development of a persistent granulomatous reaction, which can occur if the product is injected into the dermis. To prevent this, PLA should not be injected intradermally but must be injected into the subdermal plane or deeper. Otherwise, the patient can end up with visible bumps (Figure 14).

Another option for treating HIV facial lipoatrophy is to inject calcium hydroxylapatite (CaHA) (Radiesse™), a formulation of CaHA microspheres suspended in an aqueous gel carrier. A recent study was undertaken to evaluate the safety and effectiveness of soft-tissue augmentation with CaHA in patients with facial lipoatrophy secondary to HIV infection. This 12-month, open-label, prospective study enrolled 30 subjects (29 men and 1 woman) with HIV-associated facial lipoatrophy. Patients received injections of CaHA and were followed up at 3, 6, and 12 months after an initial treatment phase, which included up to 2 injections spaced 1 month apart. At the discretion of the treating physician, patients were offered touch-up injections at the 6- and 12-month follow-up visits. Measurements included changes in the Global Aesthetic Improvement Scale (GAIS), with confirmation using standardized photography and changes in skin thickness from baseline. The average initial treatment volume was 9.5 mL per patient (both sides), and total injection volumes after the full 12 months of the study (including reinjection at 12 months) averaged 16.1 mL per patient. All patients were rated as improved or better at 3, 6, and 12 months, and cheek thickness measurements substantially increased over baseline levels. The most commonly reported adverse events were edema (93%), ecchymosis (83%), and erythema (77%) (Carruthers, unpublished data).

### Table 5. Commonly Used Filler Options for HIV-Related Facial Lipoatrophy

<table>
<thead>
<tr>
<th>Product</th>
<th>Type/ Sessions</th>
<th>Approval Status</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>Nonpermanent 3-7 sessions or more needed</td>
<td>FDA approved</td>
<td>Patient assistance (under $40,000 per year income) for product only Labor cost average: $500 per session Product cost: $1000 Full price: Optimal correction will average $8000 or more, depending on severity</td>
</tr>
<tr>
<td>CaHA</td>
<td>Nonpermanent 2-3 sessions needed</td>
<td>FDA approved</td>
<td>Patient assistance available (details not available) Full price: $8000 average for optimal correction</td>
</tr>
<tr>
<td>Silicone</td>
<td>Permanent 4-6 sessions needed</td>
<td>Off-label use; FDA approved for intraocular injections to treat CMV-related retinal detachment</td>
<td>No patient assistance $1000 per session; average price for optimal correction is $6000</td>
</tr>
<tr>
<td>Polyakylimide gel</td>
<td>Permanent 1-2 sessions needed</td>
<td>Not FDA approved; Available in Europe, Canada, Mexico</td>
<td>$4500 average total cost outside US</td>
</tr>
<tr>
<td>PMMA</td>
<td>Permanent 1-2 sessions needed</td>
<td>Not FDA approved; available in Mexico, Brazil</td>
<td>$1200 average total cost outside US</td>
</tr>
</tbody>
</table>

PLA, poly-L-lactic acid; CaHA, calcium hydroxylapatite; CMV, cytomegalovirus; PMMA, polymethylmethacrylate.

*Courtesy of Nelson Vergel, BscChE, MBA.*

48. Unfortunately, a 10-mm increase in skin thickness does not necessarily correlate with an optimal cosmetic outcome. As a result, patients frequently achieve only partial improvement and are required to continue the treatment, often at a great expense. A study presented at the 14th Conference on Retroviruses and Opportunistic Infections (CROI 2007) looked at patients who had received PLA for facial lipoatrophy. Researchers used CT scans to measure how much actual change in facial volume occurred following 4 treatments. The investigators found that at week 24, in adults with facial lipoatrophy, 4 PLA treatments significantly improved both patient and physician assessments, as well as several quality-of-life domains. However, the treatment did not significantly increase facial soft-tissue volume; rather, it only modestly improved soft-tissue thickness around the injection plane. Although the use of PLA does prevent further deterioration in facial lipoatrophy, it often does not provide optimal correction of the fat loss. Therefore, it is most effective in those patients with stage 1 lipoatrophy.

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Permanent Injectable Fillers

Although the use of temporary injectable fillers effectively corrects facial wasting, many patients are looking for a permanent filler option that will eliminate the need for continual injections of temporary fillers. Liquid injectable silicone, although it has a bad reputation in the minds of much of the public, was shown many years ago to be safe for treating facial lipoatrophy. In addition, a wealth of anecdotal data suggests that it can be used safely if 3 guidelines are followed: (1) use highly purified medical grade silicone (Silikon® 1000 [purified polydimethylsiloxane], Alkon in the United States); (2) use strict microdroplet technique, defined as injecting 1/100th of a cubic centimeter into the subdermal plane at regular intervals, about 4-5 mm apart; and (3) use limited volumes at monthly treatments. If these guidelines are followed, it is estimated that adverse events (granulomatous reactions, nodule formation) will occur in <1% of patients.

A recently published protocol calls for injecting 2 mL of highly purified liquid injectable silicone (Silikon 1000) using the microdroplet technique at monthly intervals until optimal correction is achieved (Figure 15). In a pilot trial, researchers analyzed data on 77 patients whose condition had been completely corrected, in order to determine the number of treatments, amount of silicone, and time required to reach complete correction relative to initial severity. They related the number of treatments, amount of silicone, and time required to reach the end point directly to the severity of lipoatrophy ($P<.0001$). Supple, even, and natural-looking facial contours were routinely restored, and all patients tolerated treatments well. No adverse events were noted. This study demonstrated that highly purified 1000-cSt silicone oil is a safe and effective option for restoration in HIV facial lipoatrophy. Another permanent injectable option is Bio-Alcamid™, which has received a fair amount of attention from patient advocacy groups, based on positive results in a number of patients. Bio-Alcamid is composed of 3% synthetic polymer (polyalkylimide) and 97% water injected in bolus form. It remains in bolus form in the subcutis, where a fibrous capsule forms around it. One problem with this therapy is that the interior of these implants is not free from an immune system reaction, so if bacteria penetrate that area, the result can be delayed, with often massive abscess formation. Fortunately, the abscesses have been relatively easy to successfully treat with incision and drainage and antibiotic therapy.

Cosmetic Treatment Options for Lipohypertrophy

Cosmetic treatment options for lipohypertrophy are limited. One potential treatment for lipohypertrophy is deoxycholate (DOC), which is a bile salt. DOC is a fat emulsifier that can be injected subcutaneously to reduce fat stores; it is undergoing formal studies aimed at gaining FDA approval. DOC has been shown effective for reducing smaller lipomatous collections of fat, although initial evidence suggests that larger accumulations of fat in the dorsocervical area or in the submental area respond best to liposuction. Even though some surgeons argue that fat in the dorsocervical area is too fibrous to be removed with liposuction, the use of ultrasound-assisted liposuction makes removal easier.

Figure 15. Pre- and Posttreatment With Liquid Injectable Silicone

![Figure 15](image_url)

Patient had a total of 14 treatments with 24 cc total, over a 2-year period.

Photos courtesy of Derek Jones, MD.
The pathophysiological mechanisms underlying metabolic and morphologic complications of HIV and its treatment are better understood than ever before. However, there remains much that is not well understood, in large part because these complications are multifactorial, occurring in a patient population that is increasingly dealing with medical problems consistent with the aging process rather than the consequences of HIV infection. In addition, clinicians are increasingly aware that there are more ARV treatment options available for their patients. These options may be more neutral in their metabolic and morphologic effects than some of the older ARVs, at least in the short term. However, as new drugs come into greater use, clinicians must continue to be vigilant in their observation and documentation of possible metabolic and morphologic effects related to different treatment strategies.

In recent years, we have made progress in understanding the pathogenesis of lipoatrophy, but much remains to be learned. Studies have identified which ARV drugs are associated with a low or high risk of lipoatrophy: among the nucleosides, tenofovir and abacavir (combined with either lamivudine or emtricitabine) appear to be the lowest-risk nucleoside combinations. Although data on third-drug options are limited, lopinavir/ritonavir does appear to be associated with a lower risk of lipoatrophy than efavirenz. Once lipoatrophy has occurred, switching from high-risk nucleosides (e.g., stavudine and zidovudine) to low-risk NRTIs has been shown to be safe and to gradually result in increased fat stores. However, because the treatments available for lipoatrophy do not fully reverse the condition, avoiding high-risk ARV drugs is a critical first step in addressing the lipoatrophy syndrome.

In summary, when clinicians consider the problem of fat accumulation, it is important to realize that different manifestations require different treatment strategies. For localized fat accumulation (e.g., buffalo hump), surgery may be the best treatment option. In cases of visceral adiposity that appear to be associated either with particular ARV drugs or with other HIV- or non-HIV-related risk factors, lifestyle management and/or pharmacological treatments may be recommended, along with changes to a patient’s ARV regimen.

Clinicians have a responsibility to discuss the lipodystrophy syndromes with their patients when they initiate HAART, particularly if they are concerned that these syndromes will hinder their patients’ ability to adhere to treatment. Important aspects of proper management include more accurate and standardized ways of screening for morphologic changes in patients, as well as attentiveness to diagnosing the psychological disorders that are often associated with a negative body image. Further, where possible, patients should be offered effective treatment of the morphologic symptoms (either through changes to ART regimens, adjunct treatment, or surgical intervention). As we learn more about the pathogenesis of lipoatrophy and lipohypertrophy, we may be able to avoid many of these adverse effects by carefully prescribing ARV drugs and thoroughly assessing additional risk factors.
Increasingly, the lipodystrophy syndrome is being defined as 2 discrete syndromes, one being lipoatrophy and the other lipohypertrophy. For patients with lipoatrophy, clinical assessment, whether done formally or informally, is probably the most widely used diagnostic modality. Although an objective measure such as DEXA or CT scanning is valuable, these conditions are recognized in the majority of cases by patient self-report. It is becoming clear that preventing severe lipoatrophy is possible by avoiding the thymidine analogue drugs or by preemptively switching patients who have already started them to other drug combinations. What is more difficult and challenging is the management of established, clinically evident lipoatrophy. No therapy has received FDA approval for the management of either lipoatrophy or lipohypertrophy. Substitution or withdrawal of thymidine analogues is the only ART intervention that has been proved to partially restore SAT. However, the data available so far indicate that it is unlikely that patients will completely recover their fat loss, even after 10 years on a thymidine analogue–free regimen. Beyond substitution strategies, pharmacological interventions have not proved highly effective. One agent that appears promising is pioglitazone (in patients who have been taking stavudine), but it is unclear whether the conclusions drawn from subset analyses of small studies have much validity. For facial lipoatrophy, surgical treatment can successfully replace the lost fat tissue and correct the disfigurement, but the availability of those treatments is severely limited by both cost and the accessibility of experienced practitioners.

For lipohypertrophy, assessment also relies predominantly on clinical examination and patient self-reports. In terms of treatment, no strategies have yet been proved effective. The avoidance of weight gain may play a role in preventing the development of visceral adiposity, but managing dietary intake and exercise in order to avoid weight gain is a challenge, and few data support specific dietary or exercise recommendations that may prevent increases in VAT. While some potential pharmacological interventions have been shown to be effective, there are insufficient data supporting any long-term benefits. The question of whether there is truly an “HIV lipohypertrophy syndrome,” or whether the development of visceral adiposity in patients with HIV infection merely reflects larger population trends toward increasing insulin resistance and diabetes, remains unanswered. Nevertheless, the syndrome likely represents increased CV risk that needs to be addressed, in terms of both choosing an ART regimen and evaluating patients for the classic CV risk factors that are increasing in the aging HIV patient population.

Looking to the Future
The need remains to separate out the effects of long-standing HIV infection from the toxicity of ART, acknowledging the fact that many HIV patients have now been infected with this virus for 15 to 20 years. In addition, they are now 15 to 20 years older, and the natural process of aging is compounding whatever conditions arise from their HIV disease and its treatment.

We have yet to understand how much lipoatrophy will remain after we withdraw the thymidine analogues, and whether the antiretroviral drugs that we now presume to be more “lipofriendly” will remain so after 5 to 7 years of treatment. As clinicians look for new switch alternatives, they need more than ever to know the risk of metabolic side effects from the new antiretroviral drugs.

As greater numbers of HIV patients obtain care from non-HIV specialists, those clinicians will need to become more educated about the risks of HIV- and ART-associated metabolic and morphologic complications. It is particularly important among physicians caring for HIV-infected patients who are at high risk for developing CVD.

Fundamentally, our increasing focus on toxicities and complications has come about because the availability of HAART has significantly reduced the mortality associated with HIV infection in the United States and Europe. As such, the dramatic benefits of HAART have shifted the treatment of large numbers of HIV-infected individuals toward a chronic-care model and toward the management of many of the same diseases that are prevalent in the general population.
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1. Clinical evidence of lipoatrophy has been most clearly associated with which NRTI?
   A. Lamivudine  
   B. Abacavir  
   C. Stavudine  
   D. Zidovudine

2. Dual-energy X-ray absorptiometry (DEXA) assessments of trunk and limb fat changes in patients on ART (enrolled in substudy ACTG 384) have demonstrated that
   A. Lipohypertrophy and lipoatrophy are likely to result from fat redistribution from one location to the other
   B. Lipohypertrophy and lipoatrophy always occur together, although a common causal link has not been detected
   C. Patients may present with trunk and limb fat changes in the same or in opposite directions, indicating that lipohypertrophy and lipoatrophy are most likely unrelated phenomena
   D. Lipohypertrophy and lipoatrophy are undetectable during ART in previously treatment-naïve patients

3. Which antiretroviral agent is associated with the most significant effect on triglyceride and cholesterol levels?
   A. Ritonavir  
   B. Indinavir  
   C. Stavudine  
   D. Nevirapine

4. The results of the SMART trial suggest that
   A. Intermittent HAART can reduce cholesterol levels and lower the number of CVD events compared with continuous HAART
   B. Continuous HAART has no effect on cholesterol levels but appears to be associated with increased CVD events compared with intermittent HAART
   C. Intermittent HAART can reduce cholesterol levels but has no effect on CVD events compared with continuous HAART
   D. Continuous HAART is associated with a reduced risk of CVD events compared with intermittent HAART

5. Data from the FRAM study suggest that even when HIV-infected patients and their clinicians do not believe lipoatrophy is occurring, fat loss relative to HIV-negative controls can be confirmed by MRI.
   A. True  
   B. False

6. Patients with lipoatrophy who need treatment for impaired glycemic control should not be treated with
   A. Pioglitazone, because of the associated limb fat loss
   B. Metformin, because it may contribute to additional fat loss
   C. Roziglitazone, because of the associated negative impact on limb fat and cholesterol levels
   D. Any of the above

7. Reducing the risk of lipoatrophy may be possible with which of the following ART strategies?
   A. Avoiding the use of PIs
   B. Avoiding the use of NNRTIs
   C. Avoiding the use of thymidine analogues
   D. Avoiding the use of NRTIs

8. The use of adjunctive therapy with which of the following agents may have a positive impact on lipoatrophy in patients on antiretroviral therapy?
   A. Pioglitazone
   B. Rosiglitazone
   C. Metformin
   D. Testosterone

9. Data from the MACS cohort indicate a higher incidence of the metabolic syndrome among patients infected with HIV compared with those not infected, particularly in association with which of the following?
   A. Elevated triglycerides
   B. Elevated fasting glucose
   C. Reduced HDL cholesterol levels
   D. All of the above

10. Lipodystrophy is thought to be 2 aspects of a single pathologic syndrome.
    A. True
    B. False

11. According to data from the D:A:D Study Group, cardiovascular risk in HIV-infected patients treated with HAART is most strongly associated with which of the following risk factors?
    A. Exposure to HAART
    B. Previous cardiovascular disease
    C. Age
    D. Male gender

12. The results of a cross-sectional study of HIV-infected patients from the University of Washington cohort indicated that
    A. The severity of lipoatrophy had no impact on mean depression scores
    B. Health-related quality of life (HROqOL) scores were lower among patients with lipohypertrophy than among those with lipoatrophy
    C. Moderate lipoatrophy was associated with higher mean depression scores than moderate lipohypertrophy
    D. Lipohypertrophy did not appear to play a role in patient-reported HROqOL

13. In the VEGA study looking at patients with lipoatrophy, injection of poly-L-lactic acid (PLA) resulted in an increase in total cutaneous thickness of >10 mm in what percentage of patients at 96 weeks?
    A. 34%  
    B. 61%  
    C. 43%  
    D. 73%

14. The presence of lipodystrophy has not been shown to have an impact on adherence to antiretroviral therapy.
    A. True  
    B. False
**POSTTEST ANSWER FORM AND CREDIT APPLICATION**

*(Termination Date: April 1, 2009)*

**Instructions:**
- Late applications will not be accepted.
- Please anticipate 6-8 weeks after receipt of application to receive your certificate.
- Please do not use abbreviations not recognized by USPS.

Record your answers here by circling the appropriate letter.

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Please print clearly, as illegible applications will result in a delay.

**NAME**

**PROFESSION**

**LICENSE #**

**STATE OF LICENSE**

**ADDRESS (IF BUSINESS, PLEASE INCLUDE FLOOR AND/OR DEPARTMENT)**

**ADDRESS (LINE 2)**

**CITY**

**STATE**

**ZIP**

**PHONE**

**FAX**

**E-MAIL**

Please check the credit you are requesting.  

[ ] ACCME  

[ ] ANCC

I certify that I participated in: Current Perspectives on HIV-Associated Metabolic and Morphologic Abnormalities.

Please fill in the number of actual hours that you spent on this activity. Date of participation: ___________ Number of hours: ______

Signature_________________________________________________________

For you to obtain ACCME credit, 75% or more of your answers must be correct. Mail this answer sheet/credit application and evaluation form to:

Medical Education Collaborative, Inc
651 Corporate Circle, Suite 104
Golden, CO 80401
Fax: 303-420-3259
Please complete this course evaluation and mail or fax it back to Medical Education Collaborative with your completed posttest answer form. Thank you for your participation.

Please circle the answer that corresponds to your assessment of each item below.

**Were the following overall course objectives met?**

- Discuss the metabolic and morphologic complications in HIV-infected patients who are taking antiretroviral therapy
  - Yes   Somewhat   No
- Define the role of HIV treatment in the development of the lipodystrophy syndrome
  - Yes   Somewhat   No
- Describe how to manage the lipodystrophy syndrome with appropriate treatment, dietary changes, and lifestyle modifications
  - Yes   Somewhat   No

**Very**

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<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
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How would you rate the content of this activity?

- 5
- 4
- 3
- 2
- 1

How relevant was the content of this activity to your practice?

- 5
- 4
- 3
- 2
- 1

To what degree were you able to meet the learning objectives of the activity?

- 5
- 4
- 3
- 2
- 1

How would you rate this activity overall?

- 5
- 4
- 3
- 2
- 1

**Overall information and presentation provided by:**

- Julian Falutz, MD
  - 5
  - 4
  - 3
  - 2
  - 1
- Esteban Martinez, MD
  - 5
  - 4
  - 3
  - 2
  - 1
- Paul Sax, MD
  - 5
  - 4
  - 3
  - 2
  - 1
- Graeme Moyle, MD
  - 5
  - 4
  - 3
  - 2
  - 1
- Michael Stein, MD
  - 5
  - 4
  - 3
  - 2
  - 1
- Nelson Vergel, MD
  - 5
  - 4
  - 3
  - 2
  - 1
- Derek Jones, MD
  - 5
  - 4
  - 3
  - 2
  - 1

Do you believe this activity was fair, balanced, and free of commercial bias?

- Yes
- No

If no, please state the reason:

Do you feel future activities on this subject matter are necessary and/or important to your practice?

- Yes
- No

In thinking about the issues raised in this educational activity, please rate your degree of agreement with the following: I plan to implement the patient care/treatment strategies described.

- Agree
- Slightly Agree
- Neutral
- Slightly Disagree
- Disagree

If yes, please describe any changes you plan to make:

Additional comments:

Please list any other topics that would be of interest to you for future educational activities on HIV infection:

If you would like to receive information on other HIV-related CME activities, please provide your e-mail address:
Current Perspectives on HIV-Associated Metabolic and Morphologic Abnormalities

A CME/CE-Certified Enduring Material: Monograph

This activity is made available in print.
Release Date: April 1, 2008
Termination Date: April 1, 2009

This activity is jointly sponsored by Medical Education Collaborative and Healthmatters Communications.

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Please visit www.stophiv.us
A comprehensive resource for information on HIV diagnosis and prevention