Clinical Evaluation and Management of Metabolic and Morphologic Abnormalities Associated with Human Immunodeficiency Virus

Christine A. Wanke, Julian M. Falutz, Abby Shevitz, John P. Phair, and Donald P. Kotler

Tufts University School of Medicine, Boston; Montreal General Hospital, Montreal; Northwestern University Medical School, Chicago; and St. Luke’s–Roosevelt Hospital Center, New York

In recent years, a spectrum of metabolic and morphologic alterations has emerged among patients infected with human immunodeficiency virus (HIV) receiving antiretroviral treatment. Changes observed include insulin resistance, dyslipidemia, abdominal and dorsocervical fat accumulation, and fat depletion in the extremities and in the face. The health consequences of these changes are not well understood but may include increased risk for diabetes, heart disease, and stroke. Therefore, clinicians that treat patients with HIV need current, practical information on management strategies and interventions for patients with manifestations of HIV-associated lipodystrophy. Literature is reviewed on the health consequences of insulin resistance, dyslipidemia, and alterations in body fat distribution in non-HIV populations to gain perspective on how such abnormalities might affect HIV-infected patients. We also suggest treatments and strategies to manage metabolic and morphologic changes in patients with HIV.

Advances in antiretroviral therapy (ART) have markedly suppressed viral activity, improved health, and increased longevity among patients infected with HIV. But these benefits appear to have come at a price. In recent years, a spectrum of changes in body shape, fat distribution, and metabolism has emerged among HIV-infected patients, particularly those on ART. Metabolic changes observed include insulin resistance, hyperinsulinemia, and dyslipidemia [1–3]. Morphologic and fat redistribution changes include central fat accumulation and subcutaneous fat depletion [1, 4]. Although these manifestations have been grouped under the umbrella of “HIV-associated lipodystrophy syndrome” and similar terms, it is unclear whether they are separate entities or interrelated components of a single syndrome. It is equally uncertain whether some or all of the changes are caused by the virus, the treatments, or both.

Furthermore, the health consequences of the abnormalities are not fully understood. In other patient populations, visceral fat accumulation, hyperlipidemia, and insulin resistance dramatically increase the risk for diabetes, coronary heart disease (CHD), and stroke [5, 6]. Patients who develop manifestations of HIV-associated lipodystrophy syndrome may face the same health risks.

As patients live longer, clinicians need a better understanding of the mechanisms and risk factors that contribute to HIV-associated lipodystrophy. Clinicians
also need current, practical approaches for diagnosing and managing manifestations of HIV-associated lipodystrophy syndrome, along with effective and safe interventions.

One goal of this article is to consider potential health implications of various components of HIV-associated lipodystrophy syndrome. A second goal is to suggest strategies for recognizing these changes and to discuss possible interventions.

**HEALTH CONSEQUENCES IN NON–HIV-INFECTED POPULATIONS**

**Insulin resistance.** Hyperinsulinemia, which almost always indicates underlying insulin resistance [7], has been associated with various medical conditions including hypertension, CHD, and type 2 diabetes mellitus (T2DM) [7, 8]. “Insulin resistance” is defined as an impairment in normal biologic responses to insulin. Insulin resistance may result from abnormalities in β-cell products, binding of insulin to insulin antagonists, defects in insulin receptor structure or expression, or in the cellular insulin-mediated cascade. The American Diabetes Association specifies the following criteria for diabetes and impaired glucose tolerance: (1) frank diabetes: symptoms of diabetes plus random plasma glucose >200 mg/dL, or fasting plasma glucose >126 mg/dL, or 2-h plasma glucose during oral glucose tolerance testing (OGTT) >200 mg/dL; (2) impaired glucose tolerance: fasting plasma glucose, 126 mg/dL plus 2-h plasma glucose during OGTT <200 mg/dL but >140 mg/dL [8].

Epidemiologic studies have firmly established the link between hyperinsulinemia and increased cardiovascular risk. Prospective studies have shown that in people without diabetes, hyperinsulinemia increases the risk of CHD independent of other known risk factors such as obesity, hypertriglyceridemia, hypercholesterolemia, physical inactivity, hypertension, and smoking [9, 10]. Hyperinsulinemia is also associated with high triglyceride levels, increases in low-density lipoprotein (LDL) cholesterol, and decreases in high-density lipoprotein (HDL) cholesterol—all markers for increased cardiovascular risk [8, 11]. Furthermore, in vitro evidence suggests that insulin is atherogenic: it increases lipid plaque formation, stimulates smooth muscle cell proliferation, and increases cholesterol synthesis [7, 12].

Insulin resistance and impaired glucose tolerance increase cardiovascular risk [13, 14]. Glucose intolerance is associated with elevations in serum levels of tissue-type plasminogen activator antigen and plasminogen activator inhibitor-1; in turn, these are associated with an increased risk of coronary artery disease (CAD) [15].

Insulin resistance is also an independent risk factor for developing T2DM [16]. In addition to increasing the risk of microvascular damage and consequent retinopathy, nephropathy, and neuropathy, diabetes increases the risk of atherosclerotic changes that reduce blood flow to tissues and contribute to angina, heart attack, peripheral vascular disease, and stroke [17]. CHD-associated morbidity and mortality increases 2- to 4-fold among people with diabetes [18].

**Dyslipidemia.** Elevated LDL levels, with or without decreased HDL levels, are considered central to the initiation and propagation of atherosclerotic plaque and CAD [19–22]. Steadily accumulating data from epidemiologic and clinical studies have strongly and consistently associated elevated LDL and low HDL cholesterol levels with increased CHD risk. Meta-analyses of clinical trials conducted between 1970 and 1997 show that cholesterol-lowering treatments substantially and significantly decrease CHD risk, incidence, and mortality [23–28].

Elevations in lipoprotein (a) (Lp[a]) also have been associated with CAD. Lp(a) appears to be a sensitive marker of increased risk for major coronary events (i.e., myocardial infarction or sudden cardiac death) [22, 29]. In addition, Lp(a) levels appear to correlate with the severity of CAD [30].

Elevated triglycerides act synergistically with other lipid risk factors to increase the risk of CHD. For example, a large-scale prospective study has found that patients with the highest CAD risk had elevated LDL : HDL cholesterol ratios (>5) plus elevated fasting triglyceride levels (>200 mg/dL) [21, 22]. If extreme, elevated triglyceride levels may cause pancreatitis [31].

**Alterations in body fat.** Body mass index (BMI) and total fat mass are strong predictors of elevations in serum glucose levels and blood pressure [30]. Obesity contributes significantly to the development of diabetes and CAD, and many experts agree that both the location and the amount of body fat contributes to disease risk [32]. In particular, abdominal obesity has been linked to metabolic abnormalities, including elevated triglycerides, reduced HDL cholesterol, insulin resistance, hyperinsulinemia, glucose intolerance, diabetes mellitus, and premature mortality [33–39].

Both abdominal adiposity and peripheral muscle atrophy may be associated with T2DM [40]. Wasting has been associated with chronic heart failure, and peripheral atrophy may be an indicator of underlying hormonal changes associated with diabetes [41].

Associations between the accumulation of visceral adipose tissue (VAT) and disease (i.e., atherosclerosis, cardiovascular disease [CVD], stroke, and T2DM) have been recognized for many years [42–44]. Abdominal adiposity is an independent risk factor for CHD in men [6, 45] and women [46]. Central obesity—often measured in terms of elevations in waist-to-hip ratio—has been strongly linked to myocardial infarction, angina pectoris, and stroke [6, 38, 43, 47]. Excess VAT, assessed by CT scan, waist circumference, or sagittal diameter, has been shown to increase the risk for T2DM [5, 40].

**Contributing behavioral and genetic factors.** Other CVD
risk factors include excessive weight and obesity, physical inactivity, smoking, increasing age, male sex, family history, lower socioeconomic status, elevated blood pressure, and left ventricular hypertrophy. Increasing age and family history also contribute to risk for T2DM.

METABOLIC AND MORPHOLOGIC COMPLICATIONS IN PATIENTS WITH HIV INFECTION

Insulin resistance, dyslipidemia, and alterations in body fat distribution have been described in patients with HIV, more frequently in patients receiving regimens containing protease inhibitors (PIs) (hereafter referred to as "PI-containing regimens"), but also in PI-naïve people [48–53; for reviews, see 49–51]. Each abnormality may occur independently of the others; severity varies from patient to patient, and the mechanisms involved are unknown. Potential relationships among these complications, and the health risks that may be associated with them, are illustrated in figure 1.

Changes in glucose homeostasis. Early in the HIV epidemic, abnormal glucose homeostasis occurred infrequently in patients with HIV [54–56]. Later, reports of hyperglycemia and insulin resistance in patients taking PIs began to appear [2, 3, 57–64]. Frank diabetes mellitus also has been observed in patients on PI therapy, although in a relatively small percentage (1%–7%) [59, 65–68].

Overall, studies suggest that PI treatment may directly affect glucose homeostasis. Didanosine treatment also may contribute [49], and nondrug factors (e.g., viral infection or virus-related changes in immune function) may be involved. For example, Mynarcik et al. [68] documented a relationship between the degree of insulin resistance and serum levels of tumor necrosis factor in patients with HIV-associated lipodystrophy, suggesting a role for inflammatory responses in the development of the syndrome.

Hyperlactatemia. Patients on nucleoside reverse transcriptase inhibitors (NRTIs) may have chronic or acute hyperlactatemia [69, 70]. In rare instances, severe hyperlactatemia may lead to lactic acidosis, which may cause liver damage and death. Some evidence implicates NRTI-mediated mitochondrial toxicity in developing lactic acidosis [69, 71]. Whether increased lactate is associated with fat deposition or atrophy remains unclear.

Changes in serum lipid levels. Studies of patients infected with HIV showed that HDL cholesterol levels decreased soon after infection, followed by decreases in LDL cholesterol levels [72, 73]. Subsequently, with progression to AIDS, triglyceride levels were found to increase [73].

Antiretroviral agents also seem to affect serum lipid levels. Patients on PI-containing regimens often have elevated in tri-glycerides, total cholesterol, and LDL cholesterol [3, 60, 62], but HDL cholesterol levels may not change [61]. One early report noted marked hyperlipidemia in patients taking ritonavir therapy [52]. Since then, most PIs have been associated with dyslipidemia [3, 64, 74–76]. One study found that fasting triglyceride levels were 106% higher in patients on PI therapy compared with those who were not [3]. Increases in blood triglycerides, Lp(a), and apoprotein B have been seen in healthy, HIV-negative subjects after 14 days of ritonavir treatment, implicating a drug effect that is distinct from viral effects [77].

Periard et al. [76] found increased plasma levels of total and LDL cholesterol, triglycerides, and Lp(a) among 93 HIV-infected patients taking PIs. Eleven patients had elevated Lp(a) levels before PI treatment; after treatment began, these patients had a 48% increase in Lp(a). The authors suggested that Lp(a) may provide a useful marker for increased cardiovascular risk in HIV-infected patients.

Pancreatitis is more frequent in HIV-infected patients and may result from direct cytotoxic effects of antiretroviral drugs [78–81] or from drug-associated elevations in triglycerides. Some studies have associated PI-induced increases in triglycerides with pancreatitis [82, 83].

Changes in fat distribution. Body shape changes have been reported with increasing frequency among patients with HIV [3, 4, 48, 84–86]. Changes seen include fat accumulation in the abdomen and in dorsocervical ("buffalo hump") and supraclavicular regions; breast enlargement; and lipoma. Subcutaneous fat loss may also occur. Some patients have central fat accumulation only; others experience subcutaneous fat loss only; and many have both.

Risk factors for developing metabolic and morphologic changes. Research suggests that various factors—sex, age, weight, baseline BMI, change in BMI, diet, and physical activity—contribute to the risk of developing HIV-associated lipodystrophy [87, 88]. Genetic factors may also play a role [87,
Other possible factors include severity and duration of HIV infection, duration and type of ART, suppression of viremia, and lipid abnormalities before ART begins [89]. Factors that contribute to fat accumulation may differ from those contributing to fat depletion [90, 91].

**CARDIOVASCULAR RISKS IN HIV-ASSOCIATED LIPODYSTROPHY SYNDROME**

In view of the well-established relationships among dyslipidemia, insulin resistance, visceral fat accumulation, and CAD seen in non-HIV infected populations, patients with HIV-associated lipodystrophy syndrome would be expected to have increased CVD risk.

One study compared CVD risk factors in HIV-infected patients (with or without lipodystrophy, defined as clinical evidence of recent changes in body fat distribution) and healthy control subjects matched for age and BMI. Results showed HIV patients with lipodystrophy had significantly increased waist-to-hip ratio, fasting insulin levels, and diastolic blood pressure relative to control subjects. They also were more likely to have impaired glucose tolerance, diabetes, hypertriglyceridemia, and reduced HDL cholesterol. Risk factors among patients with HIV but without lipodystrophy were not significantly different from those of control subjects [92].

Sosman et al. [93] have assessed endothelial dysfunction as an indicator of atherosclerotic vascular disease in patients with HIV and identified endothelial dysfunction in patients taking PI but not other antiretroviral agents. A study by Cheminot et al. [94] demonstrated thickening of the carotid wall in patients exposed to highly active ART (HAART). Kosmiski et al. [95], by use of electron-beam CT, found early evidence of atherosclerosis in a group of 15 patients on PI therapy. The patients also had insulin resistance, increased abdominal girth, and increased VAT, as assessed by CT scans. Other investigations have found no relationship between PI use and CVD, even in patients with elevated triglyceride levels [96–100].

Anecdotal and case study reports have documented premature CAD in patients on PIs [101–104]. Two abstracts suggest an increased risk of cardiac events in large populations of HIV-infected patients. Risks included PI therapy in one study, but it also implicated routine risk factors for CHD [99, 105].

**APPROACHES TO MANAGING METABOLIC AND MORPHOLOGIC ABNORMALITIES ASSOCIATED WITH HIV INFECTION**

Making decisions regarding treatment of HIV-associated lipodystrophy is difficult, given the complexity and variety of its manifestations and the lack of information about treatment of this patient population. Discontinuing antiretroviral agents should be discouraged because it does not appear to reverse body-shape abnormalities [106, 107].

Interventions should be considered that are directed toward the specific manifestations of lipodystrophy of each individual patient. Possible interventions are discussed below and listed in Table 1, along with potential benefits and risks. All intervention data are anecdotal, and no single intervention can be uniformly recommended.

**Dietary therapy.** Dietary modification can control insulin resistance and diabetes and can improve lipid levels in overweight people [108–110]. Fat loss through diet has been shown to reduce triglyceride levels and increase HDL cholesterol levels [111, 112]. In the general population, both diet and exercise can affect both total and regional fat mass [113].

However, new research shows that the low-fat, high-carbohydrate diet often prescribed for weight loss and triglyceride reduction in patients with CVD may instead decrease HDL cholesterol levels, increase triglyceride levels, and contribute to postprandial hyperlipidemia, hyperglycemia, and hyperinsulinemia [108]. Some patients may even experience weight gain because of difficulty in achieving caloric balance and because of the potential for accelerated carbohydrate absorption [108, 114].

A diet that incorporates a moderate amount of fat and substitutes monounsaturated for saturated fatty acids may work better to reduce lipogenesis and decrease insulin resistance. In addition, including carbohydrates with a low glycemic index (those with less potential to increase insulin and glucose levels postprandially [115]) can also be of benefit, as seen in patients with T2DM [116, 117]. The impact of such a diet on adipose distribution and metabolic abnormalities in patients with HIV infection requires investigation.

**Exercise therapy.** The benefits of exercise in the general population are well known. Exercise can improve cardiovascular fitness, improve HDL and LDL cholesterol levels, increase insulin-dependent glucose uptake, and reduce abdominal fat, thereby reducing risk for CHD and diabetes [112, 118–121].

Among patients with HIV infection, exercise has no negative impact on HIV infection [122]. One small study has examined the effect of a mixed exercise program (progressive resistance training combined with an aerobic component) in patients with HIV-associated abdominal adiposity [123]. Overall, exercise reduced patients’ total body fat and trunk fat and improved strength with no adverse events [122, 123].

**Insulin-sensitizing agents.** Treatment of abnormal glucose metabolism in HIV-infected patients can, in the absence of more detailed data, follow the guidelines used for uninfected patients [124]. Often, a combination of exercise and diet is effective. Orally administered agents such as metformin and the thiazolidinediones (glitazones) also may be effective [124].

**Metformin.** Patients with diabetes who have difficulty with
Table 1. Possible management strategies for patients with lipodystrophy syndrome: potential benefits and risks.

<table>
<thead>
<tr>
<th>Treatment approach</th>
<th>Potential benefits</th>
<th>Potential risks, problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary modification</td>
<td>Improvement in insulin sensitivity</td>
<td>Limited data available for HIV-associated metabolic/morphologic abnormalities</td>
</tr>
<tr>
<td></td>
<td>Normalization of lipid profiles</td>
<td>Adherence issues</td>
</tr>
<tr>
<td></td>
<td>Reduction in excess adiposity</td>
<td>Adherence issues</td>
</tr>
<tr>
<td>Exercise</td>
<td>Improvement in insulin sensitivity</td>
<td>Injury</td>
</tr>
<tr>
<td></td>
<td>Normalization of lipid profiles</td>
<td>Excessive aerobic exercise may exacerbate lipoatrophy</td>
</tr>
<tr>
<td></td>
<td>Reduction in excess adiposity</td>
<td>Adverse drug reactions (lactic acidemia with metformin; hepatotoxicity with thiazolidinediones)</td>
</tr>
<tr>
<td>Insulin-sensitizing agents (metformin; thiazolidinediones)</td>
<td>Improvement in insulin sensitivity</td>
<td>Drug interactions</td>
</tr>
<tr>
<td></td>
<td>Control/modification of alterations in fat distribution</td>
<td></td>
</tr>
<tr>
<td>Lipid-altering agents</td>
<td>Reduction in total/LDL cholesterol</td>
<td>Hepatotoxicity, other adverse drug reactions</td>
</tr>
<tr>
<td></td>
<td>Increased HDL cholesterol</td>
<td>Drug-drug interactions: toxicity or viral rebound</td>
</tr>
<tr>
<td></td>
<td>Reduction in triglyceride levels</td>
<td></td>
</tr>
<tr>
<td>Switch therapy or PI cessation therapy</td>
<td>Improvement in insulin sensitivity</td>
<td>Development of viral resistance and loss of options for alternative antiviral regimens</td>
</tr>
<tr>
<td></td>
<td>Normalization of lipid profiles</td>
<td>Ineffective viral control; relapse</td>
</tr>
<tr>
<td></td>
<td>Reduction in total/LDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Cosmetic surgery</td>
<td>Improvement in facial appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduction in buffalo hump</td>
<td>Benefits may be temporary</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Lipolytic effects</td>
<td>Limited data on benefits</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Reduction in visceral fat, buffalo hump</td>
<td>Hyperglycemia*</td>
</tr>
<tr>
<td></td>
<td>Reduction in triglycerides and total cholesterol levels</td>
<td>Diabetes*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arthralgia*</td>
</tr>
</tbody>
</table>

NOTE. HDL, high-density lipoprotein; LDL, low-density lipoprotein; PI, protease inhibitor. * At high doses.

Glycemic control can benefit from metformin treatment [125]. Metformin acts by decreasing hepatic glucose production and increasing peripheral glucose uptake [126, 127]. As added benefits, the drug can also reduce triglyceride levels and promote modest weight loss [128, 129]. Metformin may be of value for treating changes in glucose homeostasis or body shape changes in patients with HIV. An open-label, single-arm study has tested metformin in HIV-infected patients with insulin resistance and central adiposity. The study found that 850 mg of metformin significantly decreased plasma insulin responses to oral glucose administration after 2 months of treatment. Patients who received metformin also lost weight and VAT [130].

A double-blind, placebo-controlled pilot study has assessed the safety and efficacy of metformin in HIV-infected patients with fat redistribution and insulin resistance. This study found that metformin given at a dose of 500 mg b.i.d. reduced fasting insulin levels. Metformin also reduced insulin and glucose levels during OGTT [131]. In addition, patients in the metformin group experienced significant weight loss, reductions in diastolic blood pressure, and decreases in waist circumference. Metformin had no significant effect on mean waist-to-hip ratio, systolic blood pressure, or cholesterol or triglyceride levels [131].

Some patients experience gastrointestinal intolerance at the start of metformin therapy. Rarely, patients develop lactic acidosis; those with renal dysfunction appear to be especially vulnerable [132]. Metformin may further increase the NRTI-associated risk of lactic acidosis. Because of associations between lactic acidosis and chronic liver disease, renal impairment, and cardiac failure, patients with these conditions should be carefully monitored if put on metformin treatment [132, 133].

Glitazones. Glitazones (e.g., troglitazone, rosiglitazone, pioglitazone) enhance insulin sensitivity by increasing glucose transport and adipogenesis, ultimately increasing peripheral glucose uptake. A pilot study of troglitazone in HIV-infected patients with PI-associated diabetes showed improvements in fasting glucose, postprandial glucose, and HbA1c levels after 8–12 weeks. Treatment had no significant effect on insulin sensitivity, lipid profiles, or fat distribution [134]. However, pioglitazone, but not rosiglitazone, induces CYP3A4 and may therefore decrease the effectiveness of PIs.
Rosiglitazone and pioglitazone seem to have a lower incidence of adverse effects, although 2 cases of hepatotoxicity have been reported with rosiglitazone [135, 136].

**Lipid-lowering agents.** Treatment of dyslipidemia in HIV patients can follow recommendations established by the National Cholesterol Education Program (NCEP) (table 2) [137]. Goals of these recommendations vary according to each patient’s risk category. In addition, the NCEP guidelines recommend exercise as part of any cholesterol-lowering intervention.

For patients with elevated triglycerides (200 mg/dL), NCEP guidelines recommend diet and exercise therapy. For patients with high triglycerides and other CHD risk factors, drugs should be considered when nondrug therapies do not achieve target triglyceride levels. For patients who have serum triglycerides of >1000 mg/dL, drug therapy is advisable even in the absence of high cholesterol or other CHD risk factors.

Numerous lipid-lowering agents are available if drug therapy is indicated. These include the HMG-CoA reductase inhibitors (statins), which reduce total cholesterol, LDL cholesterol, and triglycerides. Another class of agents, the fibrates, reduces triglyceride levels and may slightly reduce other cholesterol levels.

The safety and effectiveness of these agents for HIV-infected patients is under investigation [138]. One concern is the potential for interactions between the lipid-lowering agents and the antiretroviral agents. For example, PIs may increase statin levels by inhibiting CYP3A4, possibly leading to drug-related toxicity and serious adverse effects, such as rhabdomyolysis. Conversely, statins may induce cytochrome P-450 activity, thereby reducing PI concentrations and risking virologic failure [138]. Two of the fibrates—clofibrate and gemfibrozil—are metabolized by CYP3A4 and therefore may become elevated in the presence of a PI [139]. A third agent in this class, fenofibrate, does not seem to be metabolized by CYP3A4 [140].

A recent pharmacokinetic study has shown that the metabolism of most statins and fibrates, including atorvastatin, simvastatin, lovastatin, bezafibrate, and ciprofibrate, is influenced by PIs, probably through inhibitory effects on CYP3A4 [139]. Pravastatin may be the least likely of the statins to interact with CYP3A4 [139, 141].

The cardiovascular focus group of the AIDS Clinical Trials Group has begun a series of studies to examine the safety and efficacy of lipid-lowering agents. Preliminary results from a study looking at interactions between PIs and statins in HIV-negative subjects show that with PI treatment, atorvastatin and simvastatin levels increased significantly, and pravastatin levels decreased slightly. The data suggest that pravastatin is safe for use with PIs, whereas atorvastatin and simvastatin should be prescribed with caution or their doses reduced [139].

**Switch therapy.** Numerous studies have examined the effects switching PIs for non–NRTIs or NRTIs, or discontinuing PIs, in HAART regimens as a means for reversing or ameliorating metabolic changes and fat redistribution. Unfortunately, the studies are small, design and methods may vary considerably across studies, and the results are often subjective and difficult to interpret. In general, however, switch studies suggest that changing PI treatment to triple NRTI or NRTI–NRTI therapy is likely to improve metabolic parameters but unlikely to improve body-shape changes [142–148].

**Cosmetic surgery.** Cosmetic surgery (surgical resection or liposuction) has been used to treat buffalo hump; however, the hump may recur. For patients with facial wasting, facial implants (autologous fat or prosthetic material) may improve appearance, but their long-term benefit is unknown [149]. Liposuction is considered dangerous for patients with HIV-associated abdominal adiposity because HIV-associated fat deposition tends to be visceral rather than subcutaneous [150].

**Anabolic steroids.** Although studies of non–HIV-infected people show that testosterone can reduce visceral fat, lower cholesterol levels, and reduce blood pressure [151], few studies support its usefulness in treating or preventing HIV-associated lipodystrophy [152, 153]. Anabolic steroid use is associated with health risks including reduced HDL cholesterol, dyslipidemia, hepatotoxicity, and increased risk of prostatic tumor promotion [154–157].

Currently, an AIDS Clinical Trials Group study is examining the effect of testosterone treatment on metabolic and fat distribution changes over a 24-week period in HIV-infected men with abdominal obesity and mild to moderate hypogonadism.

<table>
<thead>
<tr>
<th>Table 2. National Cholesterol Education Program treatment guidelines based on low-density lipoprotein cholesterol levels.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk category</strong></td>
</tr>
<tr>
<td>Without CHD and &lt;2 risk factors</td>
</tr>
<tr>
<td>Without CHD and ≥2 risk factors</td>
</tr>
<tr>
<td>With CHD</td>
</tr>
</tbody>
</table>

**NOTE.** CHD, coronary heart disease; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol.

* Risk factors include age (men ≥45 years, women ≥65 years or with premature menopause with no estrogen replacement therapy), family history of CHD (first-degree male relative with CHD before age 55 years or first-degree female relative before 65 years), smoking currently, hypertension, low HDL cholesterol (<35 mg/dL), and diabetes mellitus. In patients with high HDL cholesterol, one risk factor can be subtracted.
Table 3. Investigational approaches to evaluating metabolic and morphologic complications in HIV-infected patients.

<table>
<thead>
<tr>
<th>Parameter, test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Fasting insulin</td>
</tr>
<tr>
<td>C peptide</td>
</tr>
<tr>
<td>Homeostatic model for insulin resistance</td>
</tr>
<tr>
<td>2-h oral glucose tolerance test</td>
</tr>
<tr>
<td>Intravenous glucose tolerance test</td>
</tr>
<tr>
<td>Intravenous insulin tolerance test</td>
</tr>
<tr>
<td>Hyperinsulinemic euglycemic clamp</td>
</tr>
<tr>
<td>Fat accumulation or depletion</td>
</tr>
<tr>
<td>Skinfold anthropometry</td>
</tr>
<tr>
<td>Sequential photography</td>
</tr>
<tr>
<td>Regional DXA*</td>
</tr>
<tr>
<td>Single-cut CT or MRI (abdominal, dorsocervical, or thoracic)</td>
</tr>
<tr>
<td>Whole-body CT or MRI</td>
</tr>
<tr>
<td>Ultrasound</td>
</tr>
<tr>
<td>Cardiac risk factors</td>
</tr>
<tr>
<td>Lp(a)</td>
</tr>
<tr>
<td>Direct LDL</td>
</tr>
<tr>
<td>Small dense LDL</td>
</tr>
<tr>
<td>Homocysteine</td>
</tr>
<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>Markers of impaired fibrinolysis (tPA, PAI-1)</td>
</tr>
<tr>
<td>Platelet reactivity</td>
</tr>
<tr>
<td>Coagulation tests</td>
</tr>
<tr>
<td>Markers of inflammation (C-reactive protein; soluble ICAM-1)</td>
</tr>
<tr>
<td>Noninvasive imaging for cardiovascular risk</td>
</tr>
<tr>
<td>B-mode carotid ultrasound</td>
</tr>
<tr>
<td>Carotid intima media thickness</td>
</tr>
<tr>
<td>Stress echocardiography</td>
</tr>
<tr>
<td>Coronary artery assessment (electron beam CT, cardiac MRI, brachial artery plethysmography)</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Lactic acid</td>
</tr>
<tr>
<td>Amylase</td>
</tr>
<tr>
<td>Liver function</td>
</tr>
</tbody>
</table>

**NOTE.**  DXA, dual-energy x-ray absorptiometry; ICAM-1, intercellular adhesion molecule 1; LDL, low-density lipoprotein; Lp(a), lipoprotein(a).

* DXA can be calibrated to assess body composition and further to assess regional (truncal vs. limb) fat and lean body mass.

**Growth hormone.** In non–HIV-infected populations, growth hormone (GH) deficiency is associated with changes in fat distribution, including increased fat mass, decreased lean body mass, and abdominal adiposity [158–160]. Some reports also associate GH deficiency with impaired glucose tolerance, increased insulin resistance, elevated total and LDL cholesterol, decreased HDL cholesterol, and vascular changes associated with arterial disease [158, 161, 162]. GH replacement therapy can reverse or ameliorate these abnormalities [161–163].

Controlled studies of GH therapy in patients with HIV-associated lipodystrophy are under way. In a study comparing HIV-infected patients with and without lipodystrophy syndrome, Rietschel et al. [164] found that increased VAT was strongly associated with reduced mean overnight GH concentrations, but not with changes in GH pulse frequency. The findings suggest that a GH secretory defect contributes to HIV-associated changes in fat distribution.

Other reports show that GH can reduce abnormal fat accumulation in HIV-infected patients [165–171]. In an open-label study of HIV-positive patients with fat redistribution syndrome, GH treatment (6 mg/day for 12 weeks) significantly reduced BMI, waist-to-hip ratio, and VAT [165]. GH treatment also reduced triglyceride and total cholesterol levels; however, fasting glucose levels increased significantly. At 6 mg per day of GH, patients reported joint stiffness, arthralgias, and fluid retention [171]. Changes in VAT reversed when GH treatment stopped [170].

Preliminary studies of lower-dose GH treatment for HIV-associated visceral adiposity have shown beneficial effects. In one study, GH given at a dose of 4 mg every other day for 24 weeks produced a 20% loss of VAT without affecting subcutaneous adipose tissue [172]. In another study, 6 months of GH treatment at 3 mg per day reduced buffalo hump and abdominal girth among patients with HIV. In this study, glucose tolerance worsened 1 month into treatment but subsequently improved (at 6 months), possibly due to reductions in visceral adiposity [173]. Additional clinical studies to characterize dose ranges and long-term efficacy of GH treatment in patients with HIV-associated central fat accumulation are under way.

**CLINICAL STRATEGIES FOR DIAGNOSING AND MONITORING MANIFESTATIONS OF HIV-ASSOCIATED LIPODYSTROPHY SYNDROME**

Although interventions for HIV-associated lipodystrophy syndrome continue to be explored, clinicians should be alert to the development of lipodystrophy in patients with HIV. We recommend developing a clinical assessment tool for routine use in HIV treatment settings.

The tool can consist of a questionnaire and a chart to be included in each patient’s file. Questions can be designed to screen for patients’ and clinicians’ observations about changes in body shape (e.g., increased abdominal girth, dorsocervical fat pads, and thinning of cheeks, limbs, or buttocks) and risk factors (e.g., smoking, hypertension, diabetes, CHD, and family history of diabetes or heart disease) that may predispose patients to lipodystrophy. Questions about relative physical activity (low, moderate, or high) and other behaviors can be included as well.

A chart can be developed to collect observations and results...
from clinical examinations and from laboratory tests. Information gathered can include weight, blood pressure, heart rate, respiration rate, waist circumference, glucose levels, and fasting lipid levels (including triglycerides and total, HDL, and LDL cholesterol levels). To screen for abnormalities in glucose homeostasis, we recommend starting with a random glucose test or a fasting glucose test. If results are abnormal (according to recommendations of the American Diabetes Association for the general population), further evaluation is needed [174], and OGTT should be performed to rule out diabetes.

To assess lipid levels, we recommend an initial fasting lipid panel, which can then be repeated every 6–12 months or with any change in ART regimen. If fasting triglycerides exceed 400 mg/dL, then treatment with lipid-lowering agents should be considered [138]. If total cholesterol levels are >200 mg/dL, treatment can follow NCEP guidelines. Measurement of direct LDL is difficult and expensive and therefore is not recommended for screening unless triglycerides levels are high, which may skew calculated LDLs.

These and other tests, listed in table 3, can be used to diagnose, characterize, or monitor morphologic and metabolic changes. However, many of these tests are research tools that are not validated for routine clinical use, and they also may be inaccessible or nonreimbursable.

The clinical assessment tool could be used at the patient’s initial visit and at each follow-up visit to gather information longitudinally. For patients with features that warrant intervention, the tool can be used to monitor responses to treatment.

CONCLUSION

Developing effective interventions that can reduce or reverse changes of HIV-associated lipodystrophy will depend on careful implementation and analysis of controlled clinical trials. As long as definitions and descriptions of HIV-associated lipodystrophy remain uncertain, such trials should focus on specific manifestations and treatment outcomes. Guidelines that include practical methods and uniform measures for diagnosing and monitoring these morphologic and metabolic changes will maximize interpretability of such clinical trials and identify which treatments can best prevent, reverse, or ameliorate manifestations of HIV-associated lipodystrophy and associated health risks. Some treatment options exist for patients with HIV-associated lipodystrophy. For now, treatment can be guided by recommendations from the literature reviewed herein.

Acknowledgments

We thank Judith A. Aberg, Ben Cheng, David A. Cooper, Ellen S. Engelson, Susan K. Fried, Joseph M. Gertner, Marshall J. Glesby, Carl Grunfeld, Steven K. Grinspoon, Thomas N. Kaku-uda, Kenneth Lichtenstein, Ariane Marelli, Kathleen Mulligan, Norma Muurahainen, and Cecilia Shikuma for their research contributions and invaluable comments on the manuscript; and Eve Wilson for her assistance in preparing the manuscript.

References

21. Assmann G, Schulte H. Relation of high-density lipoprotein choles-
terol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Prospective Cardiovascular Munster study. Am J Cardiol 1992;70:733–37.
Striker RB, Man KM, Bouvier DB, Goldberg DA, Mendiola AE.


Klein D, Hurley L, Sorel M, Sidney S. Do protease inhibitors increase the risk for coronary heart disease among HIV-positive pa-


