HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE

METABOLIC AND MORPHOLOGIC COMPLICATIONS OF HIV INFECTION

Albert J. EID, Robert ORENSTEIN

Since the introduction of highly active antiretroviral therapy (HAART) to treat HIV infection, the life expectancy of patients has dramatically increased. In this new era of HIV management, long-term morphologic and metabolic complications have superseded opportunistic infections as a major management dilemma. Physicians caring for these patients face new challenges with a limited understanding of the pathogenesis and treatment of these conditions. The range of metabolic and morphologic changes seen in today’s HIV-infected persons range from the previously recognized wasting syndrome of AIDS to lipoatrophy/lipohypertrophy, polymetabolic syndrome as well as hyperlipidemia, cardiovascular disease, lactic acidosis, and metabolic bone disease in HIV-infected patients.

1. WASTING

HIV-related wasting, characterized by marked loss of lean body mass remains a significant clinical problem in the HAART era. In the pre-HAART era, wasting was present at the time of AIDS diagnosis in 18% of patients. A more recent follow-up of a cohort of HIV-infected subjects demonstrated that 18% of patients lost > 10% of body weight over serial visits, whereas 21% lost > 5% of body weight, sustained for one year, and 8% had a body mass index (BMI) of < 20 [1]. A majority of the patients with wasting in this study were receiving HAART. In a study comparing trends in patients followed at the Johns Hopkins AIDS Service wasting was one complication that failed to decline in incidence between 1994 and 1998 [2].

Multiple definitions were proposed for wasting over time. The Consensus Development Panel Meeting in New York in July 2000 proposed the definition outlined in Table I.

Wasting with as little as 5% weight loss has been associated with increased mortality and morbidity [3-5]. It’s also associated with accelerated disease progression [3], loss of muscle protein mass, and impairment of strength and functional status [6].

Factors that contribute to wasting are inadequate food intake and absorption, untreated or incompletely-treated opportunistic infections, metabolic alterations, hypogonadism, and excessive cytokine production. The exact contribution of each of these factors to the pathogenesis of wasting is unknown.

The diagnosis of wasting is best made using bioelectrical impedance analysis (BIA) to measure changes in body cell mass (BCM), in addition to a comprehensive clinical assessment (history and physical, psychosocial evaluation, laboratory tests, dietary evaluation).

General patient management consists of simultaneous interventions to control HIV, improve immune status, correct other causes of wasting (opportunistic infection, malignancy, diarrhea), address psychosocial issues, improve nutritional intake, and treat anorexia. If wasting still persists after these interventions have been implemented, specific therapies may then be undertaken. Specific treatments for HIV-associated wasting should

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**TABLE I**

**TREATMENT GUIDELINES FOR HIV-ASSOCIATED WASTING**

<table>
<thead>
<tr>
<th>Patient must meet one of the following criteria</th>
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<tbody>
<tr>
<td>■ 10% unintentional weight loss over 12 months OR</td>
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<tr>
<td>■ 7.5% unintentional weight loss over 6 months OR</td>
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<tr>
<td>■ 5% body cell mass (BCM) loss within 6 months OR</td>
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<tr>
<td>■ Body mass index (BMI) &lt; 20 kg/m² OR</td>
</tr>
<tr>
<td>■ In men : BCM &lt; 35% body weight &amp; BMI &lt; 27 kg/m² OR</td>
</tr>
<tr>
<td>■ In women : BCM &lt; 23% body weight &amp; BMI &lt; 27 kg/m² OR</td>
</tr>
</tbody>
</table>

*Consensus Development Panel Meeting, New York, NY ; July 20, 2000.*
be individualized according to the patient’s needs. Men who are hypogonadal may benefit from testosterone replacement therapies. Recombinant human growth hormone may be helpful in patients with normal testosterone levels, in men for whom testosterone therapy is ineffective and HIV-infected women with significant wasting. Treatment with growth hormone may improve lean body mass and survival in patients with HIV-associated wasting [7-8]. Other therapeutic interventions, such as anabolic steroids (Nandrolone decanoate, Oxandrolone), progressive resistance exercise, nutritional supplements, and cytokine modulation with Thalidomide and Pentoxifylline have been effective in limited cases [9-10]. Once therapy is effective, expected clinical outcomes include the replacement of lost body cell mass and weight; improved physical capabilities, quality of life, and physical appearance; decreased frequency of opportunistic infections, hospitalizations, and related complications; and improved survival. Currently, optimal evidenced-based algorithms for treating HIV-associated wasting are not available. Some of the commonly used medications and the doses used to treat HIV-associated wasting are summarized in Table II.

2. LIPODYSTROPHY

The term lipodystrophy refers to the morphologic (fat atrophy and hypertrophy) and metabolic (dyslipidemia and insulin resistance) disturbances found in patients with HIV infection. An association between the loss of peripheral fat and the increase in central adiposity was noticed early in the HAART era. Gripshover et al. questioned this concept following a cross-sectional study where 412 HIV-positive men were compared with 153 age-matched controls. Neither self-report nor did physical examination support a correlation between peripheral fat and central fat in HIV-positive men. Therefore, to be accurate in our approach a distinction between lipoatrophy and lipohypertrophy should be made. Earlier studies of lipodystrophy lacked a unified definition, had different study designs, patient populations, prior antiretroviral drug exposure, and different methods to assess lipodystrophy. Thus, the incidence of lipodystrophy syndromes varies widely in published reports, from 2% to 83% [11]. The prevalence is reportedly higher in patients receiving combination antiretroviral therapy.

Lipoatrophy is most noticeable in the face often described as a sunken face and cabling of the limbs and a saggy buttock. Lipohypertrophy represents mainly central fat accumulation. It can also involve the breasts (particularly in women), the dorsocervical spine (buffalo hump), the muscle and the liver in addition to the formation of subcutaneous lipomas.

In a meta-analysis of nine studies assessing lipoatrophy, statistically significant risk factors were exposure to and duration of thymidine analogues with stavudine (d4T) being the most commonly involved, age (5 of 9 studies), presence of markers of disease severity (CD4/HIV RNA) (5 of 9), duration of therapy (3 of 9), and white race (3 of 9). In the eight studies assessing lipohypertrophy, the most common statistically significant risk factors were duration of therapy (3 of 8 studies), markers of disease severity (3 of 8), age (3 of 8), and protease inhibitor (PI) use (4 of 8) [12]. Table III summarizes lipoatrophy and lipohypertrophy risk factors. Another study demonstrated that men had a significantly lower adjusted risk of presenting with any alteration than women (OR : 0.47 ;

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**TABLE II**

**MEDICATIONS AND DOSES COMMONLY USED TO TREAT HIV-ASSOCIATED WASTING**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Dose/Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECOMBINANT HUMAN GROWTH HORMONE</strong></td>
<td></td>
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</tr>
<tr>
<td>Testosterone</td>
<td>50-400 mg/2-4 wks IM</td>
<td>Increases lean body mass and muscle strength in patients with HIV infection who are hypogonadal</td>
</tr>
<tr>
<td></td>
<td>5-10 gm/d gel</td>
<td></td>
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<tr>
<td></td>
<td>1 patch/d</td>
<td></td>
</tr>
<tr>
<td><strong>NANDROLONE DECANOATE</strong></td>
<td>100 mg IM q 2 wks</td>
<td>Increases in average weight gain and lean body mass</td>
</tr>
<tr>
<td><strong>OXANDROLONE</strong></td>
<td>5-20 mg/d PO</td>
<td>Increases in average weight gain and lean body mass</td>
</tr>
<tr>
<td><strong>PREDNISONE</strong></td>
<td>2.5-10 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>DRONAZINOL</strong></td>
<td>2.5-10 mg bid-tid PO</td>
<td></td>
</tr>
<tr>
<td><strong>MEGESTROL ACETATE</strong></td>
<td>400-800 mg/d PO</td>
<td></td>
</tr>
<tr>
<td><strong>CYPROHEPTADINE</strong></td>
<td>4 mg bid-qid</td>
<td>Cytokine modulation, increases body cell mass and extracellular fluid, and decreases urinary nitrogen excretion. Not approved</td>
</tr>
<tr>
<td><strong>THALIDOMIDE</strong></td>
<td>100-200 mg/d PO</td>
<td></td>
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</table>

**SC : subcutaneously**  **IM : intramuscularly**  **PO : orally**  **bid : twice daily**  **tid : three times daily**  **qid : four times daily**
95% CI: 0.38-0.58; \( P < 0.0001 \) and a significantly lower risk of lipohypertrophy \( (P = 0.0022) \) and mixed fat redistribution \( (P < 0.0001) \), whereas risk of lipoatrophy was similar between genders [13]. The presence of multiple risk factors suggests that the mechanisms for fat redistribution are likely the result of complex interactions between host, disease, and drug factors.

Data from the AIDS Clinical Trials Group (ACTG) Substudy 5005 of Study 384, a prospective, randomized, controlled trial, assessed fat redistribution in 330 antiretroviral-naive patients allocated to six different treatment arms. At weeks 48, 64, and 80, patients receiving didanosine (ddI)- stavudine (d4T) had greater decrease in limb fat than those on zidovudine (ZDV)- lamivudine (3TC). The ZDV-3TC arm had fat loss as well, although it occurred less rapidly and to a lesser extent than in the ddI-d4T arm. At week 80, patients receiving nefinavir had a more significant loss of limb fat compared to those receiving efavirenz; limb fat in the efavirenz arm also decreased, though to a lesser degree [14].

The effect of changing antiretroviral drugs on fat alterations was evaluated in multiple studies with solid evidence of partial but significant improvement of the lipoatrophy after switching thymidine analogues to abacavir [15-18].

So far, the only intervention that has been shown to (partially) reverse lipoatrophy is the discontinuation of thymidine analogues (e.g., stavudine, zidovudine), but the results obtained are partial and slow to occur [16]. There is no treatment, which will resolve lipodystrophy. Diet is of limited use, in case dietary abnormalities are present. Exercise may lead to a partial decrease in central fat accumulation and triglyceride levels, but at the expense of increased peripheral fat wasting. Reombiant Growth Hormone can be beneficial in patients with increased visceral abdominal fat and/or buffalo hump, but it is not recommended for the treatment of lipoatrophy, as it may lead to a decrease in peripheral fat and impaired glucose tolerance. Two small, uncontrolled studies suggested rosiglitazone might contribute to fat gain regardless of ongoing antiretroviral therapy. However, randomized, placebo-controlled studies have shown that rosiglitazone does not improve fat mass in HIV lipoatrophy, and may even worsen dyslipidemia despite the improvement of insulin resistance. Data from randomized studies comparing the effects of metformin, gemfibrozil and placebo in the group of patients receiving HAART found less fat loss with gemfibrozil than with placebo, and no effect of metformin [19]. Cosmetic surgery may give satisfactory esthetic results in the absence of other definitive options. Another cosmetic approach that has achieved good results is use of injections of Polylactic acid which is widely available in the US and Europe and is now FDA-approved for the treatment of facial lipoatrophy. Though cosmetic approaches may correct some of the disfigurement of lipoatrophy, the other metabolic changes continue.

3. DYSLIPIDEMIAS

Hypertriglyceridemia has been recognized in HIV-infected patients early in the epidemic but became more widely recognized with the introduction of HIV-PIs. In the pre-HAART era hypercholesterolemia was rarely a problem in HIV-infected patients. In fact, low HDL and LDL cholesterol levels were commonly observed at that time, whereas now hypercholesterolemia represents a greater problem.

In a cross-sectional study, Friis-Møller et al. [20] noted hypercholesterolemia (total cholesterol level > 240 mg/dL [6.2 mmol/L]) in 27% of subjects receiving therapy that included a PI, 23% receiving a nonnucleoside reverse-transcriptase inhibitor (NNRTI), and 10% receiving only nucleoside reverse-transcriptase inhibitors (NRTI), as compared with 8% of previously untreated subjects. The corresponding percentages for hypertriglyceridemia (triglyceride level > 200 mg/dL [2.3 mmol/L]) were 40, 32, and 23%, as compared with 15% among previously untreated subjects. Low levels of HDL cholesterol (< 35 mg/dL[0.9 mmol/L]) were reported in 27, 19, and 25% of the subjects, respectively, as compared with 26% of those who were previously untreated.

Hadigan et al. [21] showed that among patients with body-fat abnormalities, 57% had triglyceride levels > 200 mg/dL, and 46% had HDL cholesterol levels < 35 mg/dL, as compared with 9 and 17% of healthy subjects matched for age and body mass index (BMI) from the Framingham Offspring Study cohort. For cholesterol levels > 200 mg/dL (5.2 mmol/L), the prevalence rate in the HIV-infected group was 57%, as compared with 42% in the Framingham control group.

Riddler SA et al. [22] showed that there were decreases in total, HDL, and LDL cholesterol at the time of HIV infection, before treatment. With the initiation of HAART, total and LDL cholesterol increase to preinfection levels, but low HDL levels persist.

Earlier studies have incriminated the increased apo lipoprotein E levels, increased hepatic synthesis of very-low-density lipoprotein (VLDL), decreased clearance of triglycerides, acute-phase reactants, circulating cytokines, including interferon-\( \alpha \) and the viral infection

**TABLE III**

**SUMMARY OF LIPOTROPHY AND LIPOHYPERTROPHY RISK FACTORS**

<table>
<thead>
<tr>
<th>LIPOTROPHY ▼ &amp; LIPOHYPERTROPHY ▲</th>
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</thead>
<tbody>
<tr>
<td><strong>Risk Factors</strong></td>
</tr>
<tr>
<td>▼ Exposure to and duration of thymidine analogues</td>
</tr>
<tr>
<td>▼ Age</td>
</tr>
<tr>
<td>▼ Low CD4 count/ High HIV viral load</td>
</tr>
<tr>
<td>▼ Duration of therapy</td>
</tr>
<tr>
<td>▼ White race</td>
</tr>
<tr>
<td>▲ Duration of therapy</td>
</tr>
<tr>
<td>▲ Age</td>
</tr>
<tr>
<td>▲ Low CD4 count/ High HIV viral load</td>
</tr>
<tr>
<td>▲ Use of protease inhibitor</td>
</tr>
</tbody>
</table>
itself as possible contributing factors. Alterations in apolipoprotein B occur in patients receiving combination therapy (with a nucleoside analogue and a PI), mainly an increase in small, dense LDL 2 ; an increase in apolipoprotein B 3 ; and a shift toward triglyceride-rich VLDL [23]. HIV PIs also decrease proteasomal degradation of nascent lipoprotein B in vitro [24]. Furthermore, the levels of lipoprotein particles containing apolipoprotein C-III and apolipoprotein E increase in patients treated with PIs [25]. HIV treatment has also been implicated as a causative factor. PIs, most notably ritonavir, increase hepatic triglyceride synthesis and plasma triglyceride levels [26] whereas atazanavir, does not [27]. PIs also tend to increase total cholesterol levels, but this effect also varies among the individual drugs in this class [28]. HDL cholesterol levels may improve among patients who switch from a regimen based on a PI to a regimen based on other types of drugs [29].

Though the NNRTI’s, efavirenz and nevirapine may increase cholesterol levels, they predominantly increase HDL cholesterol.

No differences were observed between thymidine analogues (ZDV, D4T) or combination on cholesterol or triglyceride values during therapy [30]. Stavudine, but not tenofovir-based, antiretroviral therapy is associated with early and statistically significant increases in triglyceride and total cholesterol levels [31]. In fact, recent data presented at the International AIDS society in Brazil showed that switching from d4T to TDF was associated with statistically significant reduction in total cholesterol, triglycerides and cardiovascular risk estimated with Framingham equation.

A fasting lipid panel, consisting of triglycerides, and total, HDL, and LDL cholesterol levels, should be obtained prior to the initiation or a switch to a new antiretroviral therapy, and repeated three to six months after starting or switching therapy and then at least annually for those who remain on combination antiretroviral therapy.

The management of hyperlipidemia in HIV-infected patients is based on antiretroviral therapy modification, diet modification and the use of lipid-lowering agents.

For patients with an elevated cardiovascular risk, pre-existing hyperlipidemia, or a family history of a lipid disorder, consideration should be given to initiating or switching to PI-sparing antiretroviral regimens or atazanavir-containing regimens. However, when options are limited, antiretroviral drugs that may lead to lipid elevations should not be withheld for fear of further exacerbating lipid disorders. In the absence of results from randomized, controlled clinical trials evaluating dietary interventions in HIV-infected patients with lipid disorders, it is recommended to adopt the US National Cholesterol Education Program (NCEP) dietary guidelines for lowering cholesterol in adults [32]. Data also support the use of a Mediterranean diet (low saturated fat with monounsaturated or omega-3 polyunsaturated fat replacing some of the complex carbohydrates), in hypercholesterolemic patients. Lifestyle changes recommend-

ed for treatment of isolated hypertriglyceridemia, in addition to reduced fat intake, weight loss, and exercise, include reduction in alcohol intake. Patients with persistent high-grade hypertriglyceridemia (> 1000 mg/dL [11.3 mmol/L]) may benefit from a very low-fat diet, even if they are not overweight. Lipid-lowering agents should be considered for treatment of isolated or severe hypertriglyceridemia and/or elevated LDL and total cholesterol levels that do not respond to modification of antiretroviral therapy or therapeutic lifestyle changes, or for patients in whom such modifications are not appropriate. Recent data from the 2005 International AIDS Society Meeting in Brazil suggested that lipid management with statins is more effective than switching therapy [33].

For triglycerides, the threshold suggested for intervention is 500 mg/dL (5.6 mmol/L). Fibric acid analogues (gemfibrozil and fenofibrate) reduce triglyceride levels in HIV-1-infected patients on PIs and are the preferred initial therapy. Fenofibrate has the advantage of once daily dosing and no meal restriction (micronized form).

The HMG-CoA reductase inhibitors (statins) are effective at reducing total and LDL cholesterol levels in HIV-1-infected patients on PIs. Pravastatin, fluvastatin or atorvastatin are the preferred agents for use in HIV-1-infected patients on potent antiretroviral therapies in order to avoid drug interactions. A low starting dose should be employed (20 mg of pravastatin or 10 mg of atorvastatin once daily) followed by cautious dose escalation tailored to treatment response.

4. CARDIOVASCULAR DISEASE

The morbidity and mortality from HIV-related complications decreased significantly with the introduction of HAART. However, the evolution of dyslipidemia syndromes suggest that these patients might be at increased risk for cardiovascular events.

Data from initial retrospective studies looking at the risk of cardiovascular disease in patients on HAART were inconsistent [34-36]. Currier et al. showed that coronary heart disease incidence appears to be accelerated among young HIV-infected individuals aged 18 to 33 years [37].

To answer this question, investigators began Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study, the largest prospective study of cardiovascular risk with antiretroviral therapy. Of 23,468 patients enrolled, 126 (0.5%) had a first myocardial infarction (3.5 per 1000 person-years). Of these infarctions, 29% were fatal, representing 6% of all the deaths in the study. There were an additional 77 events related to ischemia, including coronary-artery angioplasty or bypass surgery, ischemic stroke, and carotid endarterectomy. The incidence of myocardial infarction or of any ischemic vascular event increased directly with longer exposure to antiretroviral therapy (RR 1.26 [95 % confidence interval, 1.12 to 1.41] per additional year of exposure ; P < 0.001). Too few ischemic events occurred to deter-
mine the relative risk associated with a specific antiretroviral drug class or with individual drugs. Hypercholesterolemia, older age, smoking, diabetes mellitus, male sex, and a prior history of cardiovascular disease were also associated with an increased risk of myocardial infarction. The risk of myocardial infarction in relation to the duration of antiretroviral therapy remained significant but was relatively reduced in analyses that adjusted for increased cholesterol levels, suggesting that metabolic abnormalities induced by antiretroviral therapy contributed to the increased morbidity observed [20].

Carotid intima-media thickness (IMT), used as a surrogate marker for atherosclerotic disease, was shown to be higher in HIV patients than in age-matched control subjects and progresses much more rapidly than previously reported rates in non-HIV cohorts. In HIV patients, carotid IMT is associated with classic coronary risk factors and with nadir CD4 count ≤ 200, suggesting that immunodeficiency and traditional coronary risk factors may contribute to atherosclerosis [38].

The mechanisms of vascular disease in HIV-infected patients are not known but may relate to dyslipidemia, insulin resistance, diabetes mellitus, inflammation, impaired fibrinolysis, factors specific to antiretroviral medications, or combinations of these factors.

Treatment of HIV patients with coronary artery and peripheral vascular disease should follow the same guidelines established to treat the general population.

5. INSULIN RESISTANCE/DIABETES MELLITUS

Hyperinsulinemia, and insulin resistance are commonly seen in association with fat distribution abnormalities. In addition, insulin resistance can complicate ART. Insulin resistance has been documented with most of the current PIs within a few weeks of the initiation of therapy. Among HIV-infected adults with lipodystrophy or fat accumulation, diabetes mellitus was seen in 7.0%, as compared with 0.5% of otherwise healthy control subjects matched for age and BMI. Impaired glucose tolerance was present in more than 35% of HIV-infected subjects as compared with 5% of otherwise healthy control subjects matched for age and BMI [21]. In a longitudinal cohort study, diabetes mellitus was 3.1 times as likely to develop in HIV-infected men receiving combination antiretroviral therapy as it was in control subjects over a three-year period of observation [39].

Antiretroviral therapy may alter the cellular flux of substrates (free fatty acids, accumulation of intramyocellular lipid), as well as adipokine levels (low level of adiponectin), and reduce PPAR expression in subcutaneous adipocytes. PIs induce insulin resistance in vitro. However, atazanavir and saquinavir may have minimal effects on insulin sensitivity. PIs may also reduce pancreatic β-cell insulin secretion, but insulin resistance is the primary defect.

Direct effects of nucleoside analogues on glucose metabolism have not been demonstrated, but such drugs may contribute to insulin resistance indirectly through changes in fat distribution.

Fasting glucose should be checked before and during treatment (3-6 months after starting and annually thereafter) with potent antiretroviral therapy that includes PI. In patients with insulin resistance, glucose intolerance, frank diabetes or with first-degree relatives with diabetes mellitus consideration should be given to avoiding use of a PI-based regimen as initial therapy, or to substituting alternatives to PIs if possible. Substitution of the PI component of a regimen with nevirapine, efavirenz, or abacavir has been associated with short-term improvements in insulin resistance and may be considered in this setting. For patients with persistent fasting hyperglycemia, established guidelines for treating diabetes mellitus in the general population should be followed. When drug therapy is required, consideration should be given to using insulin-sensitizing agents, such as metformin or a thiazolidinedione. Studies in small numbers of HIV-1-infected patients using metformin suggest potential benefits in reducing insulin levels, waist circumference, blood pressure, and cardiovascular risk [40-42]. Metformin should be avoided in patients with significant lipodystrophy. The thiazolidinediones increase insulin sensitivity in both non-HIV-1-infected and HIV-1-infected patients with insulin resistance and evidence of lipodystrophy. Oral hypoglycemic agents and insulin may also be appropriate for patients with more severe degrees of fasting hyperglycemia, although oral sulfonylureas, meglitinides, and related hypoglycemic agents may be of less benefit in HIV-1-infected patients with insulin resistance and may induce hypoglycemia. Insufficient evidence exists to recommend drug treatment of HIV-1-infected patients with evidence of insulin resistance who have normal fasting glucose levels.

Careful monitoring for potential adverse effects, such as hepatic dysfunction (thiazolidinediones) and lactic acidemia (metformin), is recommended after initiation of these drugs. Clinicians should inform patients about the typical symptoms of hepatic dysfunction and lactic acidemia. Liver enzymes (aspartate aminotransferase and alanine aminotransferase) should be monitored every two months for the first 12 months of thiazolidinedione treatment. Plasma lactate levels should be measured if new symptoms suggesting lactic acidemia develop during metformin treatment. Patients with significant preexisting liver disease (AST, ALT > 2.5 times the upper limit of normal [ULN]) should not take thiazolidinediones. Patients with serum creatinine above the ULN for their age or lactic acidemia (venous lactate levels > 2.0 times the ULN) should not take metformin.

6. LACTIC ACIDOSIS/HYPERLACTATEMIA

Lactic acidosis is defined as an elevated venous lactate level (> 18 mg/dL, [2 mmol/L] and low arterial pH (< 7.30). Lactic acidemia is defined as an elevated venous lactate level and normal arterial pH. Cross-sectional studies suggest that a minority of patients...
receiving nucleoside reverse transcriptase inhibitor (NRTI) therapy have asymptomatic hyperlactatemia, and a small proportion develop lactic acidosis, a rare but often fatal metabolic complication. Lactic acidemia with no or mild symptoms was detected in 8% to 21% of patients receiving at least one NRTI. Symptomatic lactic acidemia is less common occurring in about 1.5%-2.5%. Mild acidemia does not appear to predict more severe acidemia.

In moderate and severe lactic acidemia, the target organ is thought to be the liver, because of the associated biochemical, clinical, and pathologic evidence of hepatic dysfunction. It is unclear, however, whether milder lactic acidemia represents an increase in lactate production from one or more organs and/or decreased degradation.

Severe lactic acidemia is characterized by fatigue, dyspnea, weight loss, nausea, abdominal pain, and cardiac dysrhythmias. The onset is acute or subacute (median of four months in one series). Hepatic dysfunction is common and symptoms include tender hepatomegaly, peripheral edema, ascites, and encephalopathy. Jaundice is rare. Modest elevations in liver enzymes are common. Hepatic steatosis is frequently observed on imaging and biopsy, with necrosis noted in more fulminant cases. Features of chronic liver disease have not been described. Patients with low-level lactic acidemia (18-45 mg/dL [2-5 mmol/L]) may have milder constitutional and hepatic abnormalities, but are often asymptomatic.

Though originally reported with zidovudine monotherapy, this is most often seen in patients on stavudine. Nucleoside analogues inhibit reverse transcriptase replication but can also inhibit the human DNA polymerase and thereby replication of mitochondrial DNA, leading to depletion of mitochondrial DNA and drug toxicity. Mitochondrial toxicity is at least partially responsible for adverse effects such as lactic acidosis, hepatic steatosis, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, and possibly the lipodystrophy syndrome.

Routine monitoring in the absence of signs or symptoms is not recommended. Measurement is recommended in those receiving NRTIs who have clinical signs or symptoms suggestive of lactic acidemia, low bicarbonate, chloride or albumin levels, raised anion gap, unexpected increases in liver enzymes, or new onset of clinical liver failure.

In all patients with confirmed lactate levels greater than 90 mg/dL (10 mmol/L), and those with confirmed lactate levels greater than 45 mg/dL (5 mmol/L) who are symptomatic, antiretroviral therapy should be discontinued if no other cause is evident. Combination NNRTI and PI therapy can be restarted after the lactate level normalizes and the associated illness resolves. Reinstitution of alternative NRTIs in patients with prior lactic acidemia may be possible in some individuals, but should be closely monitored with lactate measured every four weeks for at least three months. For symptomatic patients whose levels are less than 45 mg/dL (5 mmol/L), continuation of NRTIs is reasonable as long as lactate levels are measured regularly.

There is no proven intervention for lactic acidemia apart from NRTI cessation. Several agents have been used with limited success for treatment of lactic acidemia in the setting of congenital mitochondrial diseases. These include essential vitamin coenzymes (thiamine and riboflavin), electron acceptors (coenzyme Q10 [ubiquinone]), antioxidants (vitamins C, E, and K), and L-carnitine. There are no data supporting a role for any of these agents in the treatment of NRTI-related lactic acidemia.

7. BONE DISORDERS

Osteopenia and Osteoporosis

Studies done prior to the advent of potent antiretroviral therapy suggested that subtle abnormalities in bone metabolism were prevalent in HIV-infected patients. Paton et al. showed marginally lower spine bone mineral density (BMD) in HIV-1-seropositive men [43]. Using dual-photon absorptiometry and dual tetrazycline labeling to study 22 antiretroviral-naïve patients, most of whom were young and underweight, Serrano et al. showed that although BMD values were similar to control group data, bone formation, turnover, and osteoclast numbers were markedly decreased, especially in those with more advanced HIV disease [44]. Knobel et al. found no BMD differences in HIV-infected patients, irrespective of the treatment or type of treatment; however, the HIV-infected patients had lower BMD compared with healthy adults [45].

Tebas et al. published the first major study of BMD in the era of potent antiretroviral therapy [46]. The prevalence of osteopenia or severe osteoporosis (Z score less than -2) were strikingly high, 50% and 21%, respectively, in those receiving PIs, compared with 23% and 11% in those not receiving PIs and 29% and 6% in control subjects. The apparent association between PI use and decreased BMD seen in the cross-sectional study by Tebas et al. was refuted in a longitudinal study by Nolan et al. [47]. Other prospective cohorts have yielded conflicting results as to whether BMD in patients receiving antiretroviral therapy increases [48] or decreases [49] over time.

Burrera et al. [50] showed a significantly lower BMD in HIV-seropositive patients in comparison with controls in lumbar spine, proximal femur and total body. There were no significant differences among treatment-naive patients and either of the treatment groups. Only time with HIV infection and not specific therapy was associated with BMD decreases. Data from the Aquitaine cohort, a large French database, was presented at the 2005 International AIDS Society Meeting in Brazil. Bone mineral density was measured in 400 consecutive HIV-infected patients (73% male; median age 43). Osteopenia and osteoporosis were present in 54.5% and 25.1% of patients respectively [51].

The question of association between lipodystrophy
and osteoporosis is still being debated. Huang et al. found that BMD was decreased in the men with lipodystrophy compared with those without, who had similar findings to the control subjects. BMD was inversely associated with visceral but not subcutaneous fat content in that study. Tebas et al. on the other hand found no relationship between the central:appendicular fat ratio and the lumbar spine or proximal femur bone mineral density t- or z-scores, suggesting that osteoporosis and body fat redistribution are independent side effects of HAART.

With consideration of all these reports, it seems that the BMD is abnormally low in a substantial proportion of HIV-infected patients, but it’s still unclear to what extent the antiretroviral therapy and mainly PIs are contributing to the bone loss.

Antiretrovirals were found to have direct effects on bone. Indinavir was found to inhibit in vitro bone-nodule formation and to inhibit the ex vivo differentiation of bone-marrow cells into osteoblasts, whereas ritonavir was found to inhibit osteoclast differentiation. Nucleoside analogs could also contribute to bone demineralization directly, through mitochondrial toxicity, or indirectly, by inducing the release of calcium hydroxyapatite from bone to buffer the lactic acid produced as a result of mitochondrial toxicity. In this regard, Carr et al. reported that osteopenia was associated with asymptomatic hyperlactatemia and lower body weight prior to starting antiretroviral therapy [52].

If reduced bone mineral density is found, an assessment for additional factors that are associated with osteopenia should be undertaken. These include thyrotoxicosis, disruption of the parathyroid hormone axis, hypogonadism, malabsorption, prolonged bed-rest, severe weight loss, alcohol intake, and medications including corticosteroids, phenobarbital, pentamidine, and ketoconazole. All patients should have an adequate dietary intake of calcium and vitamin D, and should be engaged in appropriate weight-bearing exercise. If osteoporosis is found, and in particular if a pathologic fracture occurs in the setting of osteoporosis, appropriate therapy (e.g., with a bisphosphonate drug) should be considered. Treatment with calcium, vitamin D and Alendronate has been shown to be safe and potentially beneficial in a recent study [53].

**Osteonecrosis**

Osteonecrosis, defined as an infarction at the epiphyseal or subarticular regions of bone usually resulting from circulatory insufficiency has been described as a complication of HIV-1 infection since the late 1980s [54]. The areas most often affected are the femoral and humeral heads, femoral condyles, proximal tibia, and some of the small bones in the hand and wrist. Osteonecrosis may be limited to a single site or involve several areas. Osteonecrosis has been reported with increased frequency coincident with the introduction of potent antiretroviral therapy [55-58]. Keruly et al. [59] as well as others [60] demonstrated an increased incidence of osteonecrosis over time in the Johns Hopkins HIV Clinic cohort.

Routine screening of HIV-1-infected patients for the presence of osteoporosis or osteonecrosis is not recommended. For those with symptoms of bone or joint pain or dysfunction, the diagnosis of osteonecrosis can be made by radiographic examination of the femoral head or other involved bone. MRI remains the most sensitive test to diagnose osteonecrosis. The contralateral joint should also be assessed, as bilateral disease is common. Surgical resection of involved bone and joint replacement is the only effective therapy for symptomatic osteonecrosis.

**CONCLUSIONS**

Multiple metabolic and morphologic complications have been recognized in HIV patients since the beginning of the pandemic. Because patients with HIV rapidly succumbed to opportunistic infections, less emphasis was placed on these abnormalities. Today, with the improved longevity of these patients due to potent highly active therapies, these disorders have been increasingly recognized and may now contribute to significant patient morbidity. These metabolic changes may be secondary to the HIV infection, antiretroviral therapy, the immunologic restoration or a combination of these factors. It is important for clinicians to recognize these complications as management may involve alterations in lifestyle, antiviral therapies and specific treatments directed at the metabolic consequences. Because our understanding of these long-term complications remains incomplete, there are numerous opportunities for investigation into the biologic, and immunologic basis of these as well as a host of new approaches to management. With improved understanding of their pathogenesis, new preventive models will need to be developed and tested.

**REFERENCES**


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