HIV Lipodystrophy Syndrome

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The term *HIV lipodystrophy syndrome* (HLS) was first used in 1998 by Carr et al[1] to describe morphologic and metabolic complications that occurred in individuals with HIV infection, particularly in patients on protease inhibitor (PI)–based antiretroviral therapy (ART). It is now recognized that the body fat changes (lipoatrophy and lipohypertrophy) and metabolic abnormalities (ie, dyslipidemia, insulin resistance and hyperglycemia, hyperlactatemia, lactic acidosis) associated with HLS may occur singly or in combination and are found in patients on non–PI-based ART as well as in treatment-naive patients. Of increasing importance in HIV patients is the association of accelerated atherosclerosis and increased cardiovascular morbidity and mortality with insulin resistance, dyslipidemia, and central adiposity, all components of the metabolic syndrome.[2,3] This article outlines the long-term morphologic and metabolic complications of HIV infection and ART, addresses the potential mechanisms for these complications, and reviews general screening and management considerations (**Table**). A detailed discussion of switching or adding components of ART in HIV-infected patients on long-term therapy is beyond the scope of this review.

EPIDEMIOLOGY

The exact prevalence of HIV lipodystrophy is unknown because a consensus definition for this condition is not available. An objective case definition and scoring system for HIV lipodystrophy has been proposed by the HIV Lipodystrophy Case Definition Study Group based on a case-control study of 1081 adults with HIV infection. Variables included in the scoring system were age, sex, duration of HIV infection, HIV disease clinical stage, waist/hip circumference ratio, anion gap, high-density lipoprotein (HDL) cholesterol level, percentage of leg fat, trunk/limb fat ratio, and intra-abdominal/subcutaneous abdominal fat ratio. A score of greater than 0 on the lipodystrophy scoring system is 79% sensitive and 80% specific for the diagnosis of HIV lipodystrophy.[4]

The reported prevalence of HLS ranges between 2% and 84%, depending on study criteria for lipodystrophy, type of ART, patient characteristics, duration of ART, how

TAKE HOME POINTS

- *HIV lipodystrophy syndrome* is a term used to describe body fat changes (lipoatrophy and lipohypertrophy) and metabolic abnormalities (dyslipidemia, insulin resistance and hyperglycemia, hyperlactatemia, lactic acidosis) sometimes seen in patients infected with HIV, particularly those on antiretroviral therapy (ART).
- Management options for lipoatrophy include switching ART, rosiglitazone, and cosmetic surgery.
- Management options for lipohypertrophy include lifestyle modification, switching ART, and adding pharmacotherapy, such as metformin, recombinant human growth hormone, and growth hormone–releasing hormone.
- Significant cytochrome P450 drug-drug interactions exist between protease inhibitors (PIs) and some statins (eg, simvastatin, lovastatin, atorvastatin), leading to excessive statin levels.
- Lactic acidosis is a rare but potentially fatal complication of stavudine- and didanosine-based ART.
- PI-based ART significantly increases the risk of myocardial infarction.
- Patients on ART should be screened for insulin resistance and dyslipidemia and aggressively treated if these complications develop.

lipodystrophy was measured (objectively, radiologically, or with laboratory testing), type of study, and length of the study.[5] In 494 patients on at least 1 type of PI, Martinez et al[6] found a 17% prevalence of lipodystrophy after a median follow-up of 18 months. In a study by Carr et al,[7] the prevalence of lipodystrophy was 83% in PI recipients

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Table. Diagnosis, Screening, and Management of Components of HIV Lipodystrophy Syndrome

Component	Diagnosis	Screening	Management
Lipoatrophy	Anthropometric measurements, bioelectrical impedance analysis, DEXA, CT, MRI	N/A	Switch to tenofovir- or abacavir-based ART; dermatologic/surgical implants
Lipohypertrophy	Anthropometric measurements, bioelectrical impedance analysis, DEXA, CT, MRI	N/A	Switch to non–PI-based ART (first line); lifestyle changes (diet, exercise, weight loss); and pharmacotherapy (metformin, GH analogues, if tolerated)
Dyslipidemia	Fasting lipid panel	Fasting lipid panel before initiating ART, 3–6 mo after initiation and therapy change, and annually thereafter	Lifestyle changes; for elevated LDL, statins or ezetimibe; for elevated triglycerides, fibrates and mixed statins ± fenofibrate
Insulin resistance	Fasting plasma glucose, random blood glucose, 2-hr postprandial OGTT in research setting	Fasting plasma glucose before initiating ART, 3–6 mo after initiation and therapy change, and annually thereafter	Lifestyle changes, oral hypoglycemic agents, insulin
Lactic acidosis	Measurement of arterial or central venous lactic acid	N/A	Discontinue offending medication, supportive care
Hyperlactatemia	Measurement of arterial or central venous lactic acid	N/A	Discontinue offending medication

ART = antiretroviral therapy; CT = computed tomography; DEXA = dual energy x-ray absorptiometry; GH = growth hormone; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; N/A = not applicable; OGTT = oral glucose tolerance test; PI = protease inhibitor.

versus 4% in PI-naive patients after a mean follow-up of 21 months. Veny et al[8] showed that the cumulative risk for the development of lipodystrophy after 6, 12, 18, 24, and 30 months of PI use was 3.2%, 10.7%, 29.1%, 62.5%, and 75%, respectively. However, the risk for developing lipodystrophy is not uniform for all PIs. Atazanavir is associated with a lower incidence of body fat changes and dyslipidemia compared with the older PIs (eg, nelfinavir, saquinavir). Among the nucleoside reverse transcriptase inhibitors (NRTIs), efavirenz and tenofovir are associated with a lower incidence of lipodystrophy.[9,10]

LIPOATROPHY

Lipoatrophy is the loss of subcutaneous fat in the face (malar or temporal wasting), arms, shoulders, thighs, and buttocks (peripheral wasting), often accompanied by prominent superficial veins, which produces an emaciated appearance. It is differentiated from HIV wasting in that lean body mass shows little or no decline in lipoatrophy.

Risk Factors

The use of NRTIs is associated with an increased risk of developing lipoatrophy, although PIs may also induce lipoatrophy. Among the NRTIs, stavudine is most strongly linked to lipoatrophy.[11,12] Use of stavudine in combination with didanosine is associated with severe lipoatrophy; thus, this combination is contraindicated. Other risk factors for development of lipoatrophy include increasing patient age, decrease in body mass index (BMI) before ART, prior diagnosis of AIDS, lower nadir CD4+ T-cell count, duration and severity of HIV disease, white race, male sex, and use of a PI for more than 2 years.[11]

Pathogenesis

The precise mechanism(s) underlying the development of lipoatrophy is unknown but probably involves a complex interaction of both host and environmental factors. The leading hypothesis is that NRTIs inhibit mitochondrial DNA (mtDNA) polymerase γ, an enzyme involved in replication of mtDNA.[11] This subsequently leads to depletion of mtDNA in subcutaneous adipocytes and uncoupling of oxidative phosphorylation, resulting in cellular dysfunction and increased fat cell apoptosis. PIs are thought to cause lipoatrophy by inhibiting lipogenesis and adipocyte differentiation and stimulating lipolysis. These actions may be due to inhibition of sterol regulatory element-binding protein-1 in adipocytes. The exact reason for peripheral wasting is not known, but differential autonomic innervation of various fat depots is thought to play a role.[11]

Diagnosis and Management

Diagnosis of lipoatrophy is usually clinically obvious by obtaining anthropometric measurements and can be confirmed by dual energy x-ray absorptiometry (DEXA), bioelectrical impedance analysis, computed tomography (CT), or magnetic resonance imaging (MRI). There are 3 basic treatment strategies for

lipoatrophy: (1) antiretroviral substitution, (2) addition of medications to attempt to reverse fat loss, and (3) cosmetic surgery. Some studies have shown that switching from thymidine NRTIs (eg, stavudine, zidovudine) to nonthymidine NRTIs, (eg, tenofovir, abacavir) results in a modest significant increase in limb fat mass for up to 2 years but does not result in resolution of clinical lipoatrophy.[13–17]

Several medications have been tried to reverse lipoatrophy, including anabolic steroids, L-carnitine, and rosiglitazone. However, anabolic steroids and L-carnitine have been shown to be ineffective,[18–20] and the use of rosiglitazone is controversial. In one randomized trial, patients given rosiglitazone for 48 weeks had no improvement in lipoatrophy compared with placebo-treated patients, while a smaller randomized trial showed partial correction of lipoatrophy and an increase in subcutaneous abdominal fat.[21,22] In a recent trial by Cavalcanti et al,[23] rosiglitazone had no significant effect on lipoatrophy compared with placebo in 78 patients with HIV infection.

Cosmetic surgery for facial lipoatrophy has been used, including surgically placed alloplastic, autologous, or synthetic implants; injection of temporary fillers such as poly-L-lactic acid; and injection of permanent fillers such as liquid injectable silicone.[16] In a study by Cattelan et al,[24] 4 to 6 sets of subcutaneous injections of poly-L-lactic acid over 2 to 3 months was safe and efficacious and associated with an improved quality of life.

LIPOHYPERTROPHY

Lipohypertrophy is fat accumulation that appears as abdominal visceral fat (Crix belly or protease paunch), dorsocervical fat (buffalo hump), increased neck circumference, breast hypertrophy, or lipomas. Risk factors associated with development of lipohypertrophy include increasing age, female sex, increase in BMI, PI use, and duration of ART.

Pathogenesis

HIV-1 aspartyl protease, the catalytic site of PIs, shares a 60% homology with the C-terminal region of the cellular retinoic acid-binding protein type I (CRABP-I). CRABP-I normally down-regulates apolipoprotein C III (apoC III) expression. When CRABP-I is inhibited by PIs, apoC III expression increases, which leads to impaired clearance of very low-density lipoprotein (VLDL) and the development of hypertriglyceridemia. The exact mechanism for visceral adiposity is poorly understood; however, chronic hypertriglyceridemia and increased lipid biosynthesis in the liver are thought to play a role.[5]

Diagnosis and Management

Similar to lipoatrophy, the diagnosis of lipohypertrophy is usually made by anthropometric measurements and confirmed by DEXA, bioelectrical impedance analysis, CT, or MRI. Obesity is defined as a BMI of 30 kg/m^2 or more and is not mutually exclusive of lipohypertrophy. Lipohypertrophy can be differentiated from obesity by the presence of a buffalo hump, breast hypertrophy, or lipomas. Management strategies for lipohypertrophy include lifestyle changes (eg, diet, exercise, weight loss), pharmacotherapy, and change of ART. In a study undertaken to assess the effects of weight loss in obese HIV-infected women with lipohypertrophy, a 12-week program of diet and exercise reduced adiposity in regions of subcutaneous and visceral adipose tissue.[25] Drugs that have been shown to reduce visceral adiposity include recombinant human growth hormone (rhGH), growth hormone–releasing hormone (GHRH), and metformin. In a prospective, 24-week, open-label study that assessed the efficacy of rhGH on lipodystrophy in adolescents with HIV infection, subcutaneous daily injections of rhGH (0.028 mg/kg) reduced intra-abdominal adipose tissue and increased lean mass.[26] In a randomized, double-blind, placebo-controlled trial that enrolled men with HIV lipodystrophy, GHRH significantly increased lean mass and reduced truncal and visceral fat compared with placebo.[27] However, pharmacotherapy with rhGH and GHRH is expensive, may not be well tolerated, and is significantly associated with insulin resistance.

A placebo-controlled trial of metformin therapy in patients with HLS showed a decrease in visceral abdominal fat and a proportional reduction in subcutaneous abdominal fat.[28] There are few head-to-head comparisons of metformin and rosiglitazone. A study comparing metformin and rosiglitazone in HLS showed that rosiglitazone may partly correct lipoatrophy, while metformin improved visceral fat accumulation, fasting lipid profile, and endothelial function.[15] The best management strategy may be to change the existing treatment regimen to non–PI-based ART. This underscores the need to individualize therapy in HIV-infected patients.[15,21,26–28]

DYSLIPIDEMIA
ART and Lipid Metabolism

Before the advent of ART, abnormalities of lipid metabolism were noted in HIV infection, including hypertriglyceridemia in AIDS patients, with reductions in total cholesterol, HDL cholesterol, and low-density lipoprotein (LDL) cholesterol. These changes were thought to be due to cytokine-enhanced lipogenesis as well as impaired postprandial triglyceride clearance.[29]

However, with the use of ART, the pattern of dyslipidemia changes to an even greater increase in triglycerides, reduced HDL cholesterol, and variable increases in LDL cholesterol and total cholesterol. A cohort study showed that the prevalence of dyslipidemia in patients on PI-based treatment may be as high as 44%.[30]

Each class of ART produces different effects on lipid metabolism. For PIs, ritonavir increases triglycerides, total cholesterol, and LDL cholesterol but reduces HDL cholesterol. Atazanavir increases total cholesterol and triglycerides but not as significantly as compared with nelfinavir.[31,32] In general, nonnucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with elevated HDL cholesterol and total cholesterol.[33] Among the NRTIs, stavudine is associated with hypercholesterolemia; didanosine and lamivudine do not have this effect.[34]

Reeds et al[35] found that the rate of hepatic VLDL-triglyceride secretion during fed and fasting conditions was much greater and clearance of VLDL-triglycerides from plasma was also slightly lower in men with HLS on ART compared with controls. Sekhar and colleagues[36] also found abnormal postprandial disposal and storage of chylomicron and triglyceridemia leading to persistent postprandial lipemia in men with HLS compared with controls. Both studies suggest an impairment of lipoprotein lipase activity with HIV infection and/or therapy.

Management

Management of dyslipidemia is the same in patients with HIV infection as in the general population, including LDL cholesterol goals, initiation of therapeutic lifestyle changes, and initiation of drug therapy, with no evidence to support more aggressive therapy. First, patients should be stratified based on risk factors for coronary heart disease (CHD; eg, smoking, hypertension, low HDL cholesterol, family history of CHD, age ≥ 45 yr for men and ≥ 55 yr for women). Patients with 2 or more CHD risk factors should have their 10-year risk of MI or cardiac death estimated using the Framingham risk score. Hypercholesterolemia should be managed based on National Cholesterol Education Program Adult Treatment Panel III guidelines,[37] with reduction of LDL cholesterol as a primary goal and reduction of non-HDL cholesterol as a secondary goal in patients with triglyceride levels between 200 and 499 mg/dL.

Lifestyle modifications, including increased exercise, weight loss, dietary changes, and smoking cessation, are important; however, pharmacotherapy is frequently needed to achieve LDL cholesterol goals. Statins are first-line treatment. There are potential drug interactions between some statins (ie, atorvastatin, lovastatin, simvastatin) and PIs because both are metabolized via the cytochrome P450 system, specifically isoenzyme CYP3A4. Combination treatment with a PI may result in excessively high levels of statins, leading to potentially fatal rhabdomyolysis.[38,39] Simvastatin and lovastatin should not be used with concurrent PI-based ART, and atorvastatin may be used in smaller doses. Pravastatin and fluvastatin are not metabolized by CYP3A4 and are safe to use in combination with ART.[40]

For patients with isolated hypertriglyceridemia, lifestyle modifications should be started first unless the triglyceride level is greater than 1000 mg/dL and the patient has no CHD risk factors or hypercholesterolemia or if the triglyceride level is greater than 500 mg/dL and the patient has a past history of pancreatitis. Fibrates are recommended as initial therapy for isolated fasting hypertriglyceridemia. For patients with hypercholesterolemia and hypertriglyceridemia, therapy should begin with a statin, followed by the addition of a fibrate if there is insufficient response after 3 to 4 months of treatment.

Gemfibrozil should be avoided with statin therapy (except for fluvastatin) because it inhibits glucuronidation metabolism, resulting in markedly higher statin levels and subsequently an increased risk of myopathy. Fenofibrate does not affect statin levels and is the preferable fibrate option to maximize the safety of combination therapy. Niacin may be used safely with statin therapy but is not considered first-line therapy due to the risk of insulin intolerance and liver toxicity.[41,42]

INSULIN RESISTANCE AND DIABETES

HIV-infected patients are at increased risk for developing insulin resistance and diabetes, particularly patients on PI-based therapy.[43,44] In general, more patients with HIV infection have impaired glucose tolerance (IGT) compared with overt diabetes mellitus. Carr et al[7] reported a 16% prevalence of insulin resistance and IGT as well as a 7% prevalence of diabetes among PI recipients. Development of insulin resistance varies with type of PI, with indinavir and ritonavir strongly associated with its development and amprenavir less so.[44,45] PI-associated insulin resistance and IGT are similar to that seen in type 2 diabetes. In patients with PI-induced IGT, hyperglycemia is generally not accompanied by ketosis, and oral hypoglycemic agents can be given to manage elevated glucose levels.[46] In vitro studies show that PIs directly inhibit insulin-stimulated glucose transport by the isoform transporter GLUT4, the predominant transporter involved in insulin-stimulated cellular glucose uptake in humans,

leading to insulin resistance.[47] Adiponectin is a peptide hormone secreted by adipocytes that acts primarily to increase insulin sensitivity, inhibit hepatic gluconeogenesis, and up-regulate the expression of molecules involved in fatty acid combustion. Low levels of adiponectin are inversely correlated with insulin resistance.[7] A subset of patients with predominant lipoatrophy had low levels of another adipocyte-secreted hormone, leptin. This deficiency may be important because in vitro studies of mice showed that coadministration of both leptin and adiponectin can fully normalize insulin sensitivity.[48,49]

Management

As in HIV-negative patients, lifestyle modifications, including diet, exercise, and weight loss, are the initial steps in the management of insulin resistance and diabetes in overweight patients with HIV infection. Pharmacologic therapy should be initiated if treatment goals are not achieved with diet and exercise alone. Discontinuation of PI therapy may lead to reversal of hyperglycemia.[50] However, in patients with good virologic response to current PI-based ART, pharmacotherapy can be considered rather than switching the ART regimen.

Metformin has been shown to reduce insulin resistance and related cardiovascular risk parameters in HIV-infected patients with lipodystrophy. Compared with placebo-treated patients, metformin-treated patients had a 20% decrease in insulin levels 120 minutes after a 75-g oral glucose tolerance test and experienced significant decreases in body weight and diastolic blood pressure.[28] A placebo-controlled trial of 28 HIV-infected patients showed that rosiglitazone improved insulin sensitivity and increased adiponectin levels.[51] Metformin should not be used in patients with renal failure or in patients with a history of lactic acidosis. Thiazolidinediones should be used with caution in patients with preexisting liver disease.

LACTIC ACIDOSIS

Lactic acidosis with or without hepatic steatosis and liver failure is a life-threatening condition rarely observed during NRTI use. The estimated incidence of lactic acidosis is approximately 0.85 per 1000 person-years on ART, and mortality rates vary from 33% to 57%, depending on case series.[52]

Risk Factors

The risk factor most strongly associated with lactic acidosis is NRTI use (specifically stavudine and didanosine). Other risk factors include female sex, age older than 40 years, and advanced immunosuppres-

sion.[53] NRTIs inhibit human mtDNA polymerase γ via mechanisms similar to those used to inhibit viral replication. This leads to depletion of mtDNA, resulting in derangements in oxidative phosphorylation and lactate homeostasis. NRTIs have differing affinity for mtDNA polymerase γ. Stavudine and didanosine have the highest affinity, whereas tenofovir and abacavir have the lowest (affinity of NRTIs from highest to lowest, zalcitabine > didanosine > stavudine > zidovudine > lamivudine = abacavir = tenofovir = emtricitabine).[54] The median duration of exposure to NRTIs at the time of presentation with lactic acidosis is approximately 9 months (range, 3–20 mo).[52]

Clinical Presentation and Management

Most patients with lactic acidosis present with nonspecific symptoms, such as nausea, vomiting, abdominal pain, weight loss, or weakness. Laboratory studies usually reveal a serum venous lactate level greater than 5 mmol/L, a bicarbonate level less than 20 mmol/L, an arterial pH less than 7.34, and an anion gap greater than 12. Serum lactate should be drawn into a heparinized tube containing sodium fluoride, transported to the laboratory on ice, and analyzed as soon as possible, preferably within 4 hours. If the serum lactate level is elevated, a second sample should be taken to confirm the finding.[55] Surrogate markers include elevated levels of lactate dehydrogenase, creatine kinase, amylase, lipase, and liver transaminases. Liver biopsy shows steatosis, necrosis, and inflammation.

Prompt recognition of lactic acidosis and early intervention is essential to reduce mortality. If lactate levels are greater than 5 mmol/L without symptoms or 2 to 5 mmol/L with symptoms, NRTIs and other mitochondrial toxins (eg, valproic acid, acetylsalicylic acid) should be discontinued and supportive care initiated. Supportive care includes intravenous fluids, oxygen and respiratory support, intensive care, hemodialysis, and multivitamin cocktails of riboflavin, thiamine, carnitine, coenzyme Q, and vitamin C—all of which are either cofactors in oxidative phosphorylation or antioxidants. The rationale for the use of cofactors in patients with HIV infection is the efficacy of these agents in congenital mitochondrial diseases, such as mitochondrial encephalomyopathy with lactic acidosis and stroke.[56]

After lactate levels return to normal and symptoms resolve, patients may be rechallenged with NRTI-sparing ART regimens (ie, PIs or NNRTIs), although lower affinity NRTIs, such as tenofovir, abacavir, lamivudine, and zidovudine, have been safely used with close monitoring of serum lactate levels.[55,57–59]

HYPERLACTATEMIA

In patients with HIV infection, serum lactic acid levels can be elevated without significant hepatic injury or acidosis, referred to as either asymptomatic hyperlactatemia or subclinical hyperlactatemia, depending on the presence or absence of nonspecific symptoms mentioned earlier (eg, nausea, vomiting, abdominal pain, weight loss, weakness). Symptomatic hyperlactatemia is uncommon but occurs more frequently as compared with NRTI-associated lactic acidosis. The reported incidence of symptomatic hyperlactatemia is 8 to 14.5 per 1000 person-years in patients on ART, and it carries a much better prognosis than lactic acidosis, provided that the offending NRTIs are discontinued.[52] Subclinical hyperlactatemia (ie, elevated serum lactate level without symptoms, acidosis, or liver dysfunction) occurs in 8% to 18% of HIV patients. Unlike lactic acidosis and symptomatic hyperlactatemia, NRTI use is not always the cause, and the exact etiology is unclear. A prospective cohort study showed that subclinical hyperlactatemia developed in 2% of ART-naive patients compared with 8.7% of patients on ART.[60] Routine screening of lactate levels of asymptomatic NRTI-treated patients is not warranted, since elevated lactate levels in asymptomatic patients are not predictive of mitochondrial toxicity.[55,57–59]

ART AND RISK OF MYOCARDIAL INFARCTION

Three components of HLS—insulin resistance, dyslipidemia, and central fat accumulation (lipohypertrophy)—are also components of the metabolic syndrome.[61] Cardiovascular and all-cause mortality are increased in men with the metabolic syndrome; the association is less marked for women.[62] The findings of the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group suggest that exposure to ART (specifically PIs and NRTIs) and dyslipidemia contribute to an increased risk of MI.[3,41,63] The DAD Study Group showed a 26% increase in the relative risk for MI per year of ART exposure over the first 4 to 6 years.[64] A follow-up study found that PIs but not NNRTIs significantly increased the risk of MI (relative risk/person-year, 1.16 for PIs versus 1.05 for NNRTIs).[63]

Prevention

In light of the aforementioned cardiovascular risk associated with ART, physicians must recognize HLS early, make an accurate diagnosis, and institute appropriate management to reduce cardiovascular morbidity and mortality. The New York State Department of Health AIDS Institute developed clinical guidelines for screening patients with long-term complications of ART. According to these guidelines, clinicians should assess fasting blood glucose and fasting lipid profile before initiating ART, 3 to 6 months after initiation, and annually thereafter, especially if a PI is used.[65]

CONCLUSION

According to the Centers for Disease Control and Prevention, mortality from HIV infection has declined nearly 70% since 1995, and the age-adjusted death rate from HIV/AIDS declined nearly 4% between 2000 and 2001.[66,67] These reductions can be directly attributed to ART, and as patients with HIV infection live longer, clinicians will be challenged to manage the long-term complications associated with these therapies. HLS is a syndrome of body fat changes (lipoatrophy and lipohypertrophy) and metabolic abnormalities (insulin resistance, dyslipidemia, and lactic acidosis/hyperlactatemia) seen in HIV-infected patients with variable prevalence. Risk factors for the development of HLS are frequently multifactorial, with patient demographics, type and duration of ART, and severity of HIV disease as important risk factors. Physicians managing patients with HIV infection should be cognizant of metabolic complications of ART and screen and aggressively treat patients who develop dyslipidemia and insulin resistance to reduce atherosclerosis risk. Clinicians also need to develop a high index of suspicion for development of the potentially fatal lactic acidosis in patients with nonspecific symptoms. Referral to an HIV specialist to switch ART regimens or to a dermatologist or plastic surgeon can be considered in patients who develop morphologic complications of ART. **HP**

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