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Management of the metabolic effects of HIV and HIV drugs

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Abstract

Morphologic and metabolic abnormalities, including subcutaneous adipose tissue wasting, central adipose tissue accumulation, dyslipidemia and disorders of glucose metabolism are common among HIV-infected patients receiving highly active antiretroviral therapy (HAART) and contribute to the risk of cardiovascular disease in this population. The pathogenesis of these disorders is due to complicated interactions between effects of chronic HIV infection, HAART medications, and patient factors, including genetic susceptibility. HAART has transformed HIV into a chronic condition for many patients and as a result the majority of HIV-infected patients in many areas of the developed world are 50 years. Since metabolic and cardiovascular diseases increase with aging, knowledge of the optimal management of these conditions is essential for practitioners caring for HIV-infected patients, including endocrine subspecialists. This Review highlights the clinical management of these disorders, focusing on the most recent evidence regarding the efficacy of treatment strategies, newly available medications and potential interactions between HAART medications and medications used to treat metabolic disorders.

Introduction

With the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, morbidity and mortality have decreased dramatically among HIV-infected patients.^{1,2} In the late 1990s, however, multiple morphologic and metabolic abnormalities were observed among HAART-treated patients with well-controlled HIV, including subcutaneous adipose tissue wasting (lipoatrophy), central adipose tissue accumulation (lipohypertrophy), severe dyslipidemia and abnormalities of glucose metabolism.³ The pathogenesis of these disorders is multifactorial, with varying contributions from some HAART components, chronic HIV infection, as well as behavioral and genetic factors unrelated to HIV infection. Although the direct adverse effects of HAART have lessened over the past 15 years with the introduction of less toxic HAART regimens, metabolic disorders remain a major concern for HIV-infected patients, especially since their consequences, such as cardiovascular disease, are expected to increase with the aging of the HIV population.

This Review outlines current understanding of the pathogenesis, consequences and optimal management of metabolic abnormalities among HIV-infected patients. The article will

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Competing interests

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highlight areas of particular interest to endocrinologists and other practitioners working outside the field of HIV medicine, including the role of HAART in metabolic disorders, the most recent information regarding specific therapies for metabolic complications, and potential interactions between drugs used to treat metabolic problems and HAART.

Adipose tissue changes during treatment

Body composition changes in HIV-infected individuals are often grouped under the term lipodystrophy, which includes both subcutaneous lipoatrophy and central lipohypertrophy. Despite sharing common risk factors, including older age and low nadir CD4 T-lymphocyte cell count,⁴ the pathogenesis of these two disorders is distinct and better discussed and evaluated separately. Co-occurrence of lipoatrophy and central lipohypertrophy in the same patient is best described as mixed lipodystrophy.

Lipoatrophy—Diffuse loss of subcutaneous adipose tissue that is most apparent in the face, buttocks, legs and arms is the most frequent morphologic change among HIV-infected patients receiving HAART, and affects up to one third of HAART-treated patients.^{5–7} Facial lipoatrophy, which begins in the malar region and extends to the buccal and temporal regions with increasing severity (Figure 1), can reduce quality of life and compromise adherence to HAART.⁸ Subcutaneous adipose tissue wasting is also associated with insulin resistance,⁹ dyslipidemia¹⁰ and increased systemic inflammation.¹¹

Exposure to the thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs) stavudine and zidovudine¹² is the most important risk factor for the development of lipoatrophy. These medications cause mitochondrial dysfunction in adipocytes, which leads to adipocyte apoptosis.¹³ Other components of HAART may further worsen lipoatrophy, including certain protease inhibitors, such as nelfinavir.^{14,15}

Controversy exists regarding the specific effect of the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz on limb adipose tissue. Findings of a multicenter clinical trial investigating the initiation of HAART in HIV-infected patients suggested that efavirenz was associated with a higher incidence of lipoatrophy than the protease inhibitor combination of lopinavir with ritonavir (as assessed by dual-energy x-ray absorptiometry [DXA]).¹⁵ However, this effect of efavirenz was not observed in another study of the initiation of HAART, as compared with the combination of atazanavir plus ritonavir.¹⁶ In addition, trials that have compared efavirenz with HAART regimens not based on protease inhibitor combinations, or switch studies that have compared the effects of a change to efavirenz versus continuation of protease inhibitor combinations have not demonstrated worsening lipoatrophy with efavirenz.^{17,18} Taken together, these findings argue against an independent effect of efavirenz on adipose tissue wasting.

Other patient factors, such as male sex, older age and more advanced HIV disease have also been associated with the development of lipoatrophy^{4,5,7} and certain mitochondrial haplotypes and nuclear genetic polymorphisms may increase susceptibility.^{19,20} The low incidence of lipoatrophy in HIV-infected individuals not receiving thymidine analogue NRTIs further supports the primary role of these medications in its pathogenesis.¹⁵

The most effective treatment for lipoatrophy is avoidance of or switching from treatment with thymidine analogue NRTIs.^{21–23} Fortunately, with the availability of other NRTIs without adverse effects on body composition (for example, abacavir and tenofovir disoproxil fumarate) use of thymidine analogue NRTIs has decreased considerably in the developed world.²⁴

While an increase in subcutaneous adipose tissue occurs after switching from thymidine analogue NRTIs to abacavir or tenofovir disoproxil fumarate, most evidence suggests that full restoration does not occur.^{22,25,26} In the longest of these switch studies, for example, the mean gain in extremity fat mass over 104 weeks was 1.2 kg when stavudine was replaced with abacavir.²¹ Although this gain was a mean 35% increase in extremity fat mass over the baseline measurement, it represented only a fraction of the estimated 5 to 6 kg of extremity fat that had presumably been lost during stavudine use and self-perception of the extent of lipoatrophy did not improve with the gain. For these reasons, although incident cases of lipoatrophy have decreased markedly in the past decade as stavudine and zidovudine are no longer in widespread use, lipoatrophy remains a prevalent problem among patients who have been previously exposed to thymidine analogue NRTIs.

Pharmacologic treatment of lipoatrophy has had disappointing results (Table 1). Initial enthusiasm existed regarding the use of thiazolidinediones in the management of HIV-associated lipoatrophy, bolstered by their known effects on adipocyte differentiation and proliferation,²⁷ their efficacy in congenital lipoatrophy²⁸ and promising results in initial preclinical and clinical studies.^{29,30} Over the past 10 years, however, randomized clinical trials in HIV-infected individuals have had mixed results.^{30–34} A meta-analysis of randomized clinical trials of HIV-associated lipoatrophy published in 2010 showed overall no benefit in five studies that examined the effect of rosiglitazone and a modest increase in extremity fat mass (0.35 kg over 48 weeks) in the one study that examined pioglitazone.^{35,36} The primary endpoint in these studies was DXA, a sensitive measurement of extremity fat. Even among the trials that demonstrated an increase in extremity fat by DXA, however, the change was not perceptible to the patient. Given the inconsistent benefits of thiazolidinediones in clinical trials and the potential adverse effects of long-term use, thiazolidinediones cannot be recommended for the management of lipoatrophy in HIV-infected individuals without type 2 diabetes mellitus.

The benefits of other initially promising therapies have not been substantiated on further study. The pyrimidine uridine is depleted in HIV-infected patients with lipoatrophy³⁷ and in *in vitro* models, uridine supplementation has been shown to prevent and reverse stavudine-induced mitochondrial toxicity.³⁸ Despite these results and positive pilot data,³⁹ two large, randomized clinical trials have shown no benefit of a uridine-rich supplement for the treatment of lipoatrophy in HIV-infected individuals.^{40,41} Similarly, the unexpected benefits of the 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor, pravastatin, on extremity fat recovery in a small, randomized clinical trial⁴² were not confirmed in two more recent randomized clinical trials.^{40,43} Neither uridine nor pravastatin can, therefore, be recommended for the treatment of lipoatrophy.

For patients with facial lipoatrophy that causes psychological distress, facial fillers can improve quality of life and decrease anxiety and depression symptoms.^{44–46} Both permanent and absorbable compounds have been used and should be administered by an experienced plastic surgeon or dermatologist. The use of permanent filler may be associated with infection, which may necessitate antibiotic treatment or removal of the compound.⁴⁷ Fat transplantation is another approach that has been used, but may be associated with fat hypertrophy of the transplanted fat and an undesired clinical result.⁴⁸

Recombinant leptin has been investigated as an approach to improve metabolic abnormalities among HIV-infected patients with lipoatrophy.^{49,50} Similar to the effects of recombinant leptin in congenital lipoatrophy,⁵¹ its administration in HIV-infected patients with lipoatrophy and hypoleptinemia has been associated with increased insulin sensitivity and reduced triglyceride levels in two small pilot studies.^{49,50} One study showed a 32% reduction in visceral adipose tissue, without a change in subcutaneous adipose tissue.⁵⁰

These findings provide a rationale for further investigation of the effects of recombinant leptin, particularly among patients with mixed lipodystrophy and metabolic abnormalities.

Lipohypertrophy—A subset of HIV-infected patients develop abnormal accumulation of adipose tissue, termed lipohypertrophy, typically in the setting of successful HAART. The cardinal manifestation of lipohypertrophy is a relative excess of abdominal fat in the visceral adipose tissue compartment (Figure 2). A minority of patients have coexisting dorsocervical fat pad enlargement without evidence of Cushing syndrome (Figure 1). Ectopic adipose tissue deposition in the liver, epicardium and muscle has also been associated with the quantity of visceral adipose tissue.^{52,53} Physiologically, the ectopic adipose tissue deposition may result in adverse metabolic effects, such as insulin resistance, as a result of lipotoxicity.⁵⁴

Lipohypertrophy is generally a clinical diagnosis that can be supported by anthropometric measurements. Clinical trials that have evaluated agents in the treatment of lipohypertrophy have used waist circumference and waist-to-hip ratio criteria as entry criteria.^{55,56} However, the waist-to-hip ratio will also be affected by lipotrophy in the hip region and, therefore, may not be an accurate assessment of central adiposity in an HIV-infected persons with mixed lipodystrophy. Waist circumference criteria used to define the metabolic syndrome, which differ by sex, country or ethnicity,⁵⁷ may be reasonable cut-offs, but may underestimate the volume of visceral adipose tissue in a patient with subcutaneous lipotrophy of the abdomen. Cross-sectional imaging by CT or MRI can quantify visceral adipose tissue in research settings, but a paucity of normative data limits the utility of imaging in a clinical setting. Similarly, DXA can measure changes in central versus appendicular adipose tissue in research settings but cannot distinguish between subcutaneous and visceral adipose tissue accumulation and hence is of limited clinical utility. Abdominal imaging may be useful in select cases, such as in the setting of liver disease, to distinguish ascites from lipohypertrophy.

The pathogenesis of lipohypertrophy remains elusive. No definitive evidence implicates specific antiretroviral drugs, although the AIDS Clinical Trials Group A5224s study recently reported greater increases in trunk adipose tissue and a trend towards greater increases in visceral adipose tissue in antiretroviral-naïve patients randomly allocated to atazanavir plus ritonavir compared with efavirenz.⁵⁸ In this study, which had a factorial design, trunk and visceral adipose tissue did not differ by randomization to abacavir plus lamivudine versus tenofovir plus emtricitabine. Generalized weight gain and immune reconstitution by the control of HIV replication may contribute to the pathogenesis of lipohypertrophy. Debate exists about whether the gain of central adipose tissue after initiation of HAART represents a return to health or a pathologic process. Two specific pathogenic mechanisms have been hypothesized. The first involves the dysregulation of fatty acid metabolism due to HIV or antiretroviral agents, which leads to selective deposition in the visceral adipose tissue depot in the setting of blockage of the subcutaneous depot.^{3,59} The second postulates increased local cortisol concentrations owing to aberrant conversion from cortisone.⁶⁰ Relative growth hormone deficiency may also contribute to excess visceral adipose tissue.^{61–63} Gene expression studies of dorsocervical fat pad tissue from small numbers of HIV-infected patients demonstrate increased expression of mitochondrial brown fat uncoupling protein 1 relative to that from healthy control individuals, which suggests that the adipose tissue has acquired some phenotypic features of brown fat.⁶⁴ The potential consequences of lipohypertrophy in the general population include an increased risk of coronary heart disease and type 2 diabetes mellitus.^{65,66} These adverse consequences may relate in part to associated insulin resistance and dyslipidemia as part of a metabolic syndrome.⁶⁷ Specific data on the long-term consequences of excessive visceral adipose tissue are limited in the HIV population. Abnormal adipose tissue distribution, however, has been linked to

increased stigma, diminished quality of life, and possibly decreased adherence to HAART.^{68–70} An analysis of 922 HIV-infected individuals found that patients in the highest tertile of volume of visceral adipose tissue had twice the odds of death at 5 years of follow-up compared with the lowest tertile after adjustment for HIV-related factors, cardiovascular risk factors, inflammatory markers and renal function.⁷¹ Increased volume of visceral adipose tissue may also contribute to hepatic steatosis and decreased BMD.^{72–74} These consequences merit consideration of interventions to reduce visceral adipose tissue.

Randomized controlled studies of switching specific antiretroviral agents have not had favorable effects on the volume of abdominal adipose tissue.¹⁹ An exception is a switching study of 15 HIV-infected patients with elevated insulin, total cholesterol or triglyceride levels treated with the protease inhibitor combination of lopinavir and ritonavir. This study reported a 15% reduction in visceral adipose tissue at 6 months in patients randomly allocated to switch their protease inhibitor combination to atazanavir and ritonavir versus an 11% increase in patients who did not change regimens.⁷⁵ These data require confirmation before such a strategy can be recommended.

Several small studies of lifestyle interventions, such as supervised aerobic and progressive resistance training, have reported modest, if any, reductions in abdominal adipose tissue but have yielded some improvements in associated metabolic abnormalities.^{77–79} While these trials have been disappointing, lifestyle interventions are safe and appropriate to recommend as general health measures for patients with lipohypertrophy.

A randomized placebo-controlled trial of metformin in HIV-infected patients with elevated waist-to-hip ratios and impaired glucose tolerance or hyperinsulinemia demonstrated modest reductions in abdominal adipose tissue.⁸⁰ The loss of adipose tissue, however, is not selective for the visceral compartment, and subcutaneous lipotrophy can worsen with use of metformin.^{80,81} Other trials of metformin in HIV-infected patients have not had favorable effects on visceral adipose tissue.³⁴ While data do not support recommending metformin as a specific treatment for lipohypertrophy,⁸¹ it is a reasonable pharmacologic intervention for abnormal glucose homeostasis in patients with lipohypertrophy who have impaired fasting glucose, impaired glucose tolerance or type 2 diabetes mellitus and mild or no lipotrophy.

Visceral adipose tissue area is inversely proportional to testosterone levels in men in the general population,⁸¹ and hypogonadism is common in HIV-infected men.^{83,84} However, a placebo-controlled trial of transdermal testosterone gel use in HIV-infected men with elevated waist-to-hip ratios or waist circumference and low testosterone levels reduced subcutaneous adipose tissue but not visceral adipose tissue,⁸⁵ which suggests that testosterone repletion is not indicated solely to improve body composition in this population.

Recombinant human growth hormone (rhGH) has been used to treat AIDS-related wasting and was known to be lipolytic in this setting.⁸⁶ Supraphysiologic doses of rhGH (4 mg daily or every other day) reduced visceral adipose tissue by 17–20% and improved lipid profiles in placebo-controlled trials in HIV-infected patients with abdominal obesity.^{55,87,88} Subcutaneous adipose tissue was reduced only modestly in these trials. The long-term safety of such high doses of rhGH, however, is uncertain given the associated worsening of insulin sensitivity, increased risk of developing type 2 diabetes mellitus and a high incidence of arthralgias and peripheral edema from increased tissue turgor. Lower doses of rhGH also reduce visceral adipose tissue in a dose-dependent fashion with improved tolerability.^{89,90} In a novel trial, titration of rhGH dosing to achieve insulin-like growth factor 1 (IGF-1) levels in the upper quartile of the normal range (average rhGH dose of 0.33 mg per day) resulted in an 8.5% reduction in visceral adipose tissue over 18 months with modest adverse effects on glucose homeostasis.⁹¹ Unfortunately, visceral adipose tissue re-accumulates within several

months of stopping rhGH,^{55,92} and a maintenance dose of 2 mg every other day of rhGH in one study was only marginally effective.⁵⁵

The most promising intervention for lipohypertrophy is tesamorelin, a synthetic analogue of growth hormone releasing hormone that yields more physiologic levels of IGF-1 than high-dose rhGH due to preservation of the negative feedback loop at the level of the pituitary. Two phase III, placebo-controlled trials of approximately 400 patients per study have reported 11–15% reductions in visceral adipose tissue at 6 months in the tesamorelin arms.^{93,94} In one of these trials, re-randomization of patients in the tesamorelin arm to continue tesamorelin for an additional 6 months versus placebo resulted in an overall reduction in visceral adipose tissue of 17.5% in the active arm while visceral adipose tissue returned to baseline in the placebo arm.⁹⁴ Limb adipose tissue and subcutaneous adipose tissue were reduced only modestly by tesamorelin, while lipid profiles tended to improve. The most common adverse effects were injection site erythema, pruritus and hypersensitivity skin reaction. About half of the patients treated with tesamorelin in a phase II trial developed IgG antibodies against tesamorelin at week 26, the clinical significance of which is unknown.⁹³ No differences were found in IGF-1 levels or changes in visceral adipose tissue by IgG status. Mild deterioration in glucose tolerance has also been observed with tesamorelin therapy.⁹⁵

Many unanswered questions exist concerning the optimal use of tesamorelin, including whether intermittent therapy or an induction–maintenance approach could be clinically useful or whether long-term administration is required to maintain the reduction in visceral adipose tissue. The long-term safety of elevating IGF-1 levels in this setting is unknown, but the potential associations between IGF-1 levels and risk of malignancies in the general population^{96,97} and the increased predisposition of HIV-infected patients to certain malignancies are of concern.⁹⁸ A summary of the treatment strategies for central lipohypertrophy is presented in Table 1.

Dyslipidemia

Untreated, advanced HIV infection is characterized by hypertriglyceridemia, low concentrations of HDL cholesterol and LDL cholesterol and a predominance of small LDL particles.^{99,100} Untreated, less advanced HIV disease may be associated with lower concentrations of HDL particles^{101,102} in association with elevated inflammatory markers.¹⁰²

Effective HAART seems to result in a return of total cholesterol and LDL cholesterol to the premorbid state, in what has been termed a return to health phenomenon.¹⁰³ This phenomenon probably only constitutes a part of what is observed with initiation of HAART since specific drug regimens can result in different effects on lipids. HDL cholesterol levels may increase in patients treated with HAART, although the effects have been variable in different studies perhaps as a function of the treatment regimen.

The effects of individual antiretroviral agents on lipid parameters have been difficult to ascertain since drugs are typically given in three-drug combinations. Limited data from healthy volunteers who received short courses of single drugs indicate that several protease inhibitor drugs elevate triglyceride levels in the absence of HIV.^{104,105} Most protease inhibitors are taken with a low dose of ritonavir, a protease inhibitor that is used as a pharmacokinetic enhancer to boost levels of the co-administered active protease inhibitor. Ritonavir-boosted protease inhibitors commonly result in elevations of triglyceride levels. LDL cholesterol levels increase with most contemporary HAART regimens, which may largely be due to the patient's improved health status.¹⁰⁶ Use of the NNRTIs efavirenz and nevirapine is associated with significant elevations in levels of HDL cholesterol.¹⁰⁷

Tenofovir, a nucleotide analogue, seems to reduce levels of non-HDL cholesterol, LDL cholesterol and total cholesterol even when added to a fully suppressive HAART regimen.¹⁰⁸

Guidelines based on expert opinion advocate measurement of fasting lipids in HIV-infected patients annually and before and after changing HAART regimens.¹⁰⁹ Management of dyslipidemia and targeting of lipid levels follow guidelines from the general population.^{109,110} Risk stratification based on the Framingham risk equation seems to underestimate coronary heart disease event rates in HIV-infected patients but only modestly;¹¹¹ investigators have derived an HIV-specific equation that requires further validation.¹¹² Whether HIV-infected patients should be managed more aggressively owing to their chronic inflammatory state and perceived increased risk of coronary heart disease is an open question.

If lifestyle intervention fails to achieve appropriate lipid goals, clinicians have the option of switching HAART regimens or adding lipid-lowering therapy. Randomized controlled trials have demonstrated beneficial effects on lipid profiles from switching certain protease inhibitors to alternative agents.^{23,113–118} Clinicians and patients, however, may be reluctant to switch effective HIV therapies due to concerns about potential loss of virologic control and new adverse effects. Some clinicians favor the addition of a lipid-lowering agent despite the added pill burden and cost since the clinical efficacy of some such agents are proven in the general population and some may have pleiotropic effects. The efficacy of lipid-lowering therapy in HIV-infected individuals may, however, be lower than that in the general population.¹¹⁹

When hypertriglyceridemia predominates, fibrates, fish oil supplementation or extended release niacin are all effective in HIV-infected patients.^{120–125} Similarly, statins are effective at lowering LDL cholesterol,^{120,126–128} with the caveat that important drug–drug interactions exist between some statins and antiretroviral drugs (Table 2). Lovastatin and simvastatin should not be co-administered with protease inhibitors because of the potential for substantial elevations in statin exposure.¹²⁹ Pravastatin exposure does not increase with co-administered protease inhibitors, with the exception of darunavir; darunavir and pravastatin should, therefore, not be co-administered.^{130,131} Atorvastatin and rosuvastatin exposure increase modestly with some protease inhibitors and can be administered safely starting at low doses.^{129,132,133} Data on efavirenz use suggest that NNRTIs lower exposure to statins, which may necessitate the use of increased doses.¹³⁴

Insulin resistance and T2DM

The risk of insulin resistance and type 2 diabetes mellitus is increased in HIV-infected patients receiving HAART compared to HIV-seronegative control individuals in some cohorts.^{135,136} In the Multicenter AIDS Cohort Study, for example, the incidence of type 2 diabetes mellitus was more than four times greater in HIV-infected men receiving HAART than in HIV-seronegative control participants.¹³⁵ Certain protease inhibitors have been shown to reversibly induce insulin resistance through the inhibition of glucose translocation through GLUT4.¹³⁷ The thymidine analogue NRTIs, which lead to lipodystrophy as reviewed above, also have direct effects on glucose metabolism by inducing mitochondrial dysfunction.^{138,139} Exposure to HAART may also lead to insulin resistance indirectly, through effects on regional body adipose tissue changes, inflammation and adipokine and free fatty acid dysregulation.

Chronic HIV infection and the resulting systemic inflammation can also lead to insulin resistance and type 2 diabetes mellitus among HIV-infected individuals. In the Multicenter AIDS Cohort Study, higher levels of insulin resistance markers were observed in all groups

of HIV-infected men than in HIV-uninfected control participants, even among those who were not receiving HAART, which suggests an effect of HIV infection itself.¹⁴⁰ In another study, markers of systemic inflammation 48 weeks after HAART initiation, particularly increased tumor necrosis factor activity, were associated with an increased risk of incident type 2 diabetes mellitus.¹⁴¹

Screening for diabetes mellitus in HIV-infected patients is currently recommended before HAART initiation, from 3–6 months after initiation and annually thereafter.^{142,143} In the general population, HbA_{1c} has recently been recommended for screening of diabetes mellitus.¹⁴⁴ In HAART-treated, HIV-infected individuals, however, HbA_{1c} may underestimate glucose exposure,¹⁴⁵ which could potentially lead to underdiagnosis if HbA_{1c} is used as the sole diagnostic criteria. In one study, HbA_{1c} underestimated average blood glucose by approximately 1.7 mmol/l (approximately 1.0 HbA_{1c} percentage points),¹⁴⁶ although this was not confirmed in a study of HIV-infected women.¹⁴⁷ Thereasons underlying the potential inaccuracy of HbA_{1c} in HIV-infected individuals require further study. Factors associated with discordance between actual and predicted HbA_{1c} include higher mean corpuscular volume, current NRTI use, and, in particular, abacavir use.¹⁴⁶ Because of the potential inaccuracy of HbA_{1c}, fasting plasma glucose test or 2-h plasma glucose values after an oral glucose challenge should continue to be the diagnostic tests of choice for HIV-infected patients.

The choice of treatment for type 2 diabetes mellitus should follow recommendations in the general population. Lifestyle modification is an essential part of diabetes therapy for HIV-infected individuals and results in a significant reduction in HbA_{1c}.¹⁴⁸ As in the general population, metformin should be considered first-line therapy in those without a contraindication, particularly in those with central lipohypertrophy in whom reductions in visceral adipose tissue may be enhanced.¹⁴⁹ In patients with lipodystrophy and type 2 diabetes mellitus, pioglitazone may be a preferred option, since metformin may exacerbate lipodystrophy. However, the potential benefits of pioglitazone on glycemic control and modest effects on subcutaneous adipose tissue needs to be weighed against the possibility of fluid retention, increased risk of bladder cancer, and decreased BMD and fracture.¹⁵⁰ The last two considerations are especially important in that the risk of osteoporosis and fracture is higher in HIV-infected individuals compared with HIV-uninfected individuals.^{151,152} No known pharmacologic interactions exist between HAART and anti-diabetic medications. One exception is the newly approved dipeptidyl peptidase IV inhibitor, saxagliptin, which is metabolized by cytochrome P450 3A4 and, therefore, should be avoided or the dosage should be reduced in ritonavir-treated patients.

In HIV-infected patients with impaired fasting glucose or impaired glucose tolerance, lifestyle modification is the first-line treatment. Similar to the general population, pharmacologic treatment of prediabetes with metformin can be considered, especially in those patients <60 years of age with a BMI ≥ 35 kg/m².¹⁵³ Among HIV-infected patients, it is also reasonable to consider metformin in a patient with impaired fasting glucose or impaired glucose tolerance who also has central adipose tissue accumulation.

Managing cardiovascular risk

Metabolic abnormalities in HIV-infected patients may contribute to an increased risk of cardiovascular disease, compared with that in the general population.¹⁵⁷ In addition, certain components of HAART and chronic HIV infection may have more direct effects on cardiovascular risk.^{155–157} Exposure to certain protease inhibitors and abacavir have been associated with cardiovascular events, but these data are controversial.^{158,159}

Current data also indicate that cardiovascular events in HIV-infected patients are closely associated with traditional cardiovascular risk factors,¹⁶⁰ which may be more common in the HIV-infected population. Cigarette smoking, for example, is highly prevalent in HIV-infected cohorts,^{161,162} and is closely associated with cardiovascular events. Importantly, smoking cessation also leads to a reduction in cardiovascular events among HIV-infected individuals and is, therefore, a crucial target for intervention.¹⁶² Hypertension is another modifiable cardiovascular risk factor that is more prevalent in some HIV-infected populations¹⁶³ and should be managed similarly to that in the general population.¹⁶⁴ Aspirin should be given for secondary prevention of cardiovascular disease and for primary prevention in accordance with current recommendation in the general population until more data are available.¹⁶⁵ Further research is required to determine whether the risks and benefits of aspirin therapy are similar to those in the HIV-uninfected population.

Unanswered questions

Role of inflammation—Data in the past few years indicate that residual inflammation and immune activation may occur in patients with suppressed HIV viremia receiving HAART and in so-called ‘elite controllers’ who are able to control HIV replication without the use of antiretroviral therapy.^{166–168} The residual inflammation may be due to the host response to persistent viral reservoirs, the loss of integrity of the gut mucosa owing to CD4 depletion and resulting microbial translocation,¹⁶⁹ or the reactivation of other latent viruses, such as cytomegalovirus.¹⁷⁰ Whether this inflammatory response contributes to the pathogenesis of some of the metabolic complications discussed above is uncertain. Strategies aimed at mitigating end-organ complications, such as atherosclerosis, by targeting inflammation (for example with statins) are being studied.

Effect of new antiretroviral drugs—Limited studies of drugs in new classes of antiretroviral agents, such as integrase inhibitors and CCR5 inhibitors, suggest that they do not adversely affect lipids or insulin sensitivity, although data are lacking on body composition. Ongoing clinical trials with metabolic and body adipose tissue assessments, including some with measurements of carotid intima-media thickness and brachial artery reactivity, will clarify whether contemporary HAART regimens have more favorable safety profiles than previously used HAART regimens.

Effect of Earlier HIV Treatment—The potential for uncontrolled HIV replication and immune dysregulation to contribute to the pathogenesis of complications such as atherosclerosis has contributed to changes in treatment guidelines that favor earlier initiation of HAART (namely, at a higher CD4 cell count than previously). An ongoing randomized trial of immediate versus deferred initiation of HAART for patients with CD4 cell counts >500 cells/mm³ may shed light on the risks versus benefits of earlier initiation of HIV therapy in relation to metabolic complications.

Conclusions

With the advent of effective antiretroviral therapy, the life expectancy of HIV-infected individuals is approaching that of their HIV-uninfected counterparts. Owing to effects of HAART and chronic HIV infection, body adipose tissue changes, dyslipidemia and glucose abnormalities are common among HIV-infected patients. However, HAART-specific metabolic toxicities have decreased with the availability of agents with fewer glucose and lipid effects. Nonetheless, the consequences of metabolic abnormalities, which include an increased risk of type 2 diabetes mellitus and cardiovascular disease, remain a major concern among HIV-infected patients, particularly since these diseases increase in frequency with aging. Current strategies to decrease cardiometabolic risk in HIV-infected patients

mirror those in the general population and include aggressive treatment of modifiable risk factors. Potential interactions between HAART and medication to treat metabolic disease, such as certain statin medications, should also be kept in mind when treating HIV-infected individuals. The long-term benefits and risks of tesamorelin, the newly approved agent to treat central lipohypertrophy require clarification. Further research is needed to understand the role of chronic inflammation in the pathogenesis of metabolic and cardiovascular disease, to evaluate the effect of new antiretroviral agents and to identify other treatment strategies.

Review criteria

The Review was based on the authors' personal collection of publications and conference abstracts concerning lipoatrophy, lipohypertrophy, insulin resistance, dyslipidemia and cardiovascular risk among HIV-infected individuals. Searches based on these search terms were made in PubMed up to December 2010. In addition, supplemental PubMed searches were performed using the terms "thiazolidinedione AND HIV" and "growth hormone AND HIV AND lipodystrophy". Only English language articles were selected for this Review.

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Reference List

1. Palella FJ Jr, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998; 338:853–860. [PubMed: 9516219]
2. Detels R, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA*. 1998; 280:1497–1503. [PubMed: 9809730]
3. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet*. 1998; 352:1881–1883. [PubMed: 9652687]
4. Lichtenstein KA, et al. Incidence of and risk factors for lipoatrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. *J Acquir Immune Defic Syndr*. 2003; 32:48–56. [PubMed: 12514413]
5. Jacobson DL, et al. Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. *Clin Infect Dis*. 2005; 40:1837–1845. [PubMed: 15909274]
6. Tien PC, Grunfeld C. What is HIV-associated lipodystrophy? Defining fat distribution changes in HIV infection. *Curr Opin Infect Dis*. 2004; 17:27–32. [PubMed: 15090886]
7. Miller J, et al. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. *HIV Med*. 2003; 4:293–301. [PubMed: 12859330]
8. Santos CP, et al. Self-perception of body changes in persons living with HIV/AIDS: prevalence and associated factors. *AIDS*. 2005; 19(Suppl 4):S14–21. S14–S21. [PubMed: 16249648]
9. Mynarcik DC, McNurlan MA, Steigbigel RT, Fuhrer J, Gelato MC. Association of severe insulin resistance with both loss of limb fat and elevated serum tumor necrosis factor receptor levels in HIV lipodystrophy. *J Acquir Immune Defic Syndr*. 2000; 25:312–321. [PubMed: 11114831]
10. Wohl D, et al. The Associations of Regional Adipose Tissue With Lipid and Lipoprotein Levels in HIV-Infected Men. *J Acquir Immune Defic Syndr*. 2008; 48:44–52. [PubMed: 18360291]
11. Vigouroux C, et al. Serum adipocytokines are related to lipodystrophy and metabolic disorders in HIV-infected men under antiretroviral therapy. *AIDS*. 2003; 17:1503–1511. [PubMed: 12824788]

12. Bogner JR, et al. Stavudine versus zidovudine and the development of lipodystrophy. *J Acquir Immune Defic Syndr*. 2001; 27:237–244. [PubMed: 11464142]
13. Cherry CL, et al. Tissue-specific associations between mitochondrial DNA levels and current treatment status in HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2006; 42:435–440. [PubMed: 16810110]
14. Dube MP, et al. Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides. *AIDS*. 2005; 19:1807–1818. [PubMed: 16227788]
15. Haubrich RH, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. 2009; 23:1109–1118. [PubMed: 19417580]
16. McComsey, G., et al. Bone and Limb Fat Outcomes of ACTG A5224s, a Substudy of ACTG A5202: A Prospective, Randomized, Partially Blinded Phase III Trial of ABC/3TC or TDF/FTC with EFV or ATV/r for Initial Treatment of HIV-1 Infection. ed. 17th Conference on Retroviruses & Opportunistic Infections (CROI 2010); San Francisco. February 16–19, 2010; 2010. p. Abstract 106LB
17. Lennox JL, et al. Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *J Acquir Immune Defic Syndr*. 2010; 55:39–48. [PubMed: 20404738]
18. Drechsler H, Powderly WG. Switching effective antiretroviral therapy: a review. *Clin Infect Dis*. 2002; 35:1219–1230. [PubMed: 12410482]
19. Hulgán T, et al. European mitochondrial DNA haplogroups and metabolic changes during antiretroviral therapy in AIDS Clinical Trials Group Study A5142. *AIDS*. 2011; 25:37–47. [PubMed: 20871389]
20. Montes AH, et al. The MMP1 (-16071G/2G) single nucleotide polymorphism associates with the HAART-related lipodystrophic syndrome. *AIDS*. 2010; 24:2499–2506. [PubMed: 20852404]
21. Martin A, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS*. 2004; 18:1029–1036. [PubMed: 15096806]
22. McComsey GA, et al. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. *Clin Infect Dis*. 2004; 38:263–270. [PubMed: 14699460]
23. Moyle GJ, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. *AIDS*. 2006; 20:2043–2050. [PubMed: 17053350]
24. Easterbrook PJ, et al. Patterns and predictors of the use of different antiretroviral drug regimens at treatment initiation in the UK. *HIV Med*. 2008; 9:47–56. [PubMed: 18199172]
25. Moyle G, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. *AIDS*. 2006; 20:2043–50. [PubMed: 17053350]
26. Martin A, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS*. 2004; 18:1029–1036. [PubMed: 15096806]
27. Adams M, et al. Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. *J Clin Invest*. 1997; 100:3149–3153. [PubMed: 9399962]
28. Arioglu E, et al. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med*. 2000; 133:263–274. [PubMed: 10929166]
29. Caron M, et al. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes*. 2001; 50:1378–1388. [PubMed: 11375339]
30. Hadigan C, et al. Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized, controlled trial. *Ann Intern Med*. 2004; 140:786–794. [PubMed: 15148065]

31. Carr A, et al. No effect of rosiglitazone for treatment of HIV-1 lipodystrophy: randomised, double-blind, placebo-controlled trial. *Lancet*. 2004; 363:429–438. [PubMed: 14962523]
32. Sutinen J, et al. Rosiglitazone in the treatment of HAART-associated lipodystrophy--a randomized double-blind placebo-controlled study. *Antivir Ther*. 2003; 8:199–207. [PubMed: 12924536]
33. Mulligan K, et al. Effects of Metformin and Rosiglitazone on Body Composition in HIV-infected Patients with Hyperinsulinemia and Elevated Waist/Hip Ratio: A Randomized, Placebo-controlled Trial. *AIDS*. 2007 Jan 2; 21(1):47–57. [PubMed: 17148967]
34. Schindler K, et al. The effect of rosiglitazone on insulin sensitivity, beta cell function, bone mineral density, and body composition in hiv-positive patients on highly-active antiretroviral therapy (HAART). *Horm Metab Res*. 2009; 41:573–579. [PubMed: 19322744]
35. Raboud JM, et al. A meta-analysis of six placebo-controlled trials of thiazolidinedione therapy for HIV lipodystrophy. *HIV Clin Trials*. 2010; 11:39–50. [PubMed: 20400410]
36. Slama L, et al. Effect of pioglitazone on HIV-1-related lipodystrophy: a randomized double-blind placebo-controlled trial (ANRS 113). *Antivir Ther*. 2008; 13:67–76. [PubMed: 18389900]
37. Domingo P, et al. Uridine metabolism in HIV-1-infected patients: effect of infection, of antiretroviral therapy and of HIV-1/ART-associated lipodystrophy syndrome. *PLoS ONE*. 2010; 5:e13896. [PubMed: 21085568]
38. Walker UA, et al. Uridine abrogates mitochondrial toxicity related to nucleoside analogue reverse transcriptase inhibitors in HepG2 cells. *Antivir Ther*. 2003; 8:463–470. [PubMed: 14640394]
39. Sutinen J, et al. Uridine supplementation for the treatment of antiretroviral therapy-associated lipodystrophy: a randomized, double-blind, placebo-controlled trial. *Antivir Ther*. 2007; 12:97–105. [PubMed: 17503753]
40. Calmy A, et al. No significant effect of uridine or pravastatin treatment for HIV lipodystrophy in men who have ceased thymidine analogue nucleoside reverse transcriptase inhibitor therapy: a randomized trial. *HIV Med*. 2010; 11:493–501. [PubMed: 20236365]
41. McComsey GA, et al. Uridine supplementation in the treatment of HIV lipodystrophy: results of ACTG 5229. *AIDS*. 2010; 24:2507–2515. [PubMed: 20827170]
42. Mallon PW, et al. Effect of pravastatin on body composition and markers of cardiovascular disease in HIV-infected men--a randomized, placebo-controlled study. *AIDS*. 2006; 20:1003–1010. [PubMed: 16603852]
43. Macallan DC, et al. Treatment of altered body composition in HIV-associated lipodystrophy: comparison of rosiglitazone, pravastatin, and recombinant human growth hormone. *HIV Clin Trials*. 2008; 9:254–268. [PubMed: 18753120]
44. Moyle GJ, Brown S, Lysakova L, Barton SE. Long-term safety and efficacy of poly-L-lactic acid in the treatment of HIV-related facial lipodystrophy. *HIV Med*. 2006; 7:181–185. [PubMed: 16494632]
45. Carey DL, et al. A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipodystrophy. *J Acquir Immune Defic Syndr*. 2007; 46:581–589. [PubMed: 18193500]
46. Loutfy MR, et al. Immediate versus delayed polyalkylimide gel injections to correct facial lipodystrophy in HIV-positive patients. *AIDS*. 2007; 21:1147–1155. [PubMed: 17502725]
47. Guaraldi G, et al. Surgical correction of HIV-associated facial lipodystrophy. *AIDS*. 2011; 25:1–12. [PubMed: 20975513]
48. Guaraldi G, et al. Facial lipohypertrophy in HIV-infected subjects who underwent autologous fat tissue transplantation. *Clin Infect Dis*. 2005; 40:e13–e15. [PubMed: 15655734]
49. Magkos F, et al. Leptin replacement improves postprandial glycemia and insulin sensitivity in human immunodeficiency virus-infected lipodystrophic men treated with pioglitazone: a pilot study. *Metabolism*. 2010
50. Mulligan K, et al. The Effects of Recombinant Human Leptin on Visceral Fat, Dyslipidemia, and Insulin Resistance in Patients with HIV-Associated Lipodystrophy and Hypoleptinemia. *J Clin Endocrinol Metab*. 2009
51. Oral EA, et al. Leptin-replacement therapy for lipodystrophy. *N Engl J Med*. 2002; 346:570–578. [PubMed: 11856796]

52. Torriani M, Hadigan C, Jensen ME, Grinspoon S. Psoas muscle attenuation measurement with computed tomography indicates intramuscular fat accumulation in patients with the HIV-lipodystrophy syndrome. *J Appl Physiol*. 2003; 95:1005–1010. [PubMed: 12766180]
53. Lo J, et al. Increased epicardial adipose tissue volume in HIV-infected men and relationships to body composition and metabolic parameters. *AIDS*. 2010; 24:2127–2130. [PubMed: 20588167]
54. Villarroya F, Domingo P, Giralt M. Lipodystrophy in HIV 1-infected patients: lessons for obesity research. *Int J Obes (Lond)*. 2007
55. Grunfeld C, et al. Recombinant human growth hormone to treat HIV-associated adipose redistribution syndrome: 12 week induction and 24-week maintenance therapy. *J Acquir Immune Defic Syndr*. 2007; 45:286–297. [PubMed: 17592343]
56. Falutz J, et al. A placebo-controlled, dose-ranging study of a growth hormone releasing factor in HIV-infected patients with abdominal fat accumulation. *AIDS*. 2005; 19:1279–1287. [PubMed: 16052083]
57. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006; 23:469–480. [PubMed: 16681555]
58. McComsey GA, et al. Peripheral and Central Fat Changes in Subjects Randomized to Abacavir-Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. *Clin Infect Dis*. 2011; 53:185–96. [PubMed: 21690627]
59. Sekhar RV, et al. Metabolic basis of HIV-lipodystrophy syndrome. *Am J Physiol Endocrinol Metab*. 2002; 283:E332–E337. [PubMed: 12110539]
60. Sutinen J, et al. In the lipodystrophy associated with highly active antiretroviral therapy, pseudo-Cushing's syndrome is associated with increased regeneration of cortisol by 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue. *Diabetologia*. 2004; 47:1668–1671. [PubMed: 15455200]
61. Koutkia P, Canavan B, Breu J, Grinspoon S. Growth hormone (GH) responses to GH-releasing hormone-arginine testing in human immunodeficiency virus lipodystrophy. *J Clin Endocrinol Metab*. 2005; 90:32–38. [PubMed: 15483073]
62. Koutkia P, Meininger G, Canavan B, Breu J, Grinspoon S. Metabolic regulation of growth hormone by free fatty acids, somatostatin, and ghrelin in HIV-lipodystrophy. *Am J Physiol Endocrinol Metab*. 2004; 286:E296–E303. [PubMed: 14559725]
63. Rietschel P, et al. Assessment of growth hormone dynamics in human immunodeficiency virus-related lipodystrophy. *J Clin Endocrinol Metab*. 2001; 86:504–510. [PubMed: 11158000]
64. Guallar JP, et al. Differential gene expression indicates that 'buffalo hump' is a distinct adipose tissue disturbance in HIV-1-associated lipodystrophy. *AIDS*. 2008; 22:575–584. [PubMed: 18316998]
65. Yusuf S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004; 364:937–952. [PubMed: 15364185]
66. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. *Am J Clin Nutr*. 2006; 84:483–489. [PubMed: 16960160]
67. Hadigan C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis*. 2001; 32:130–139. [PubMed: 11118392]
68. Ammassari A, et al. Relationship between HAART adherence and adipose tissue alterations. *J Acquir Immune Defic Syndr*. 2002; 31 (Suppl 3):S140–S144. [PubMed: 12562038]
69. Reynolds NR, Neidig JL, Wu AW, Gifford AL, Holmes WC. Balancing disfigurement and fear of disease progression: Patient perceptions of HIV body fat redistribution. *AIDS Care*. 2006; 18:663–673. [PubMed: 16971273]
70. Blanch J, et al. Factors associated with severe impact of lipodystrophy on the quality of life of patients infected with HIV-1. *CID*. 2004; 38:1464–1470.
71. Scherzer R, et al. Decreased Limb Muscle and Increased Central Adiposity Are Associated with 5-Year All-cause Mortality in HIV Infection. *AIDS*. 2011 [Epub ahead of print].

72. Huang JS, Rietschel P, Hadigan CM, Rosenthal DI, Grinspoon S. Increased abdominal visceral fat is associated with reduced bone density in HIV-infected men with lipodystrophy. *AIDS*. 2001; 15:975–982. [PubMed: 11399979]
73. Tien PC, et al. Regional adipose tissue and elevations in serum aminotransferases in HIV-infected individuals. *JAIDS*. 2008; 48:169–176. [PubMed: 18285711]
74. Ryan P, et al. Predictors of severe hepatic steatosis using abdominal ultrasound in HIV-infected patients. *HIV Med*. 2009; 10:53–59. [PubMed: 19018879]
75. Stanley TL, et al. Effects of switching from lopinavir/ritonavir to atazanavir/ritonavir on muscle glucose uptake and visceral fat in HIV-infected patients. *AIDS*. 2009; 23:1349–1357. [PubMed: 19474651]
76. Thoni GJ, et al. Reduction of fat accumulation and lipid disorders by individualized light aerobic training in human immunodeficiency virus infected patients with lipodystrophy and/or dyslipidemia. *Diabetes Metab*. 2002; 28:397–404. [PubMed: 12461477]
77. Dolan SE, et al. Effects of a supervised home-based aerobic and progressive resistance training regimen in women infected with human immunodeficiency virus: a randomized trial. *Arch Intern Med*. 2006; 166:1225–1231. [PubMed: 16772251]
78. Fitch KV, et al. Effects of a lifestyle modification program in HIV-infected patients with the metabolic syndrome. *AIDS*. 2006; 20:1843–1850. [PubMed: 16954725]
79. Hadigan C, et al. Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. *JAMA*. 2000; 284:472–477. [PubMed: 10904511]
80. Kohli R, Shevitz A, Gorbach S, Wanke C. A randomized placebo-controlled trial of metformin for the treatment of HIV lipodystrophy. *HIV Med*. 2007; 8:420–426. [PubMed: 17760733]
81. Sheth SH, Larson RJ. The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials. *BMC Infect Dis*. 2010; 10:183. [PubMed: 20573187]
82. Seidell JC, Bjorntorp P, Sjostrom L, Kvist H, Sannerstedt R. Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. *Metabolism*. 1990; 39:897–901. [PubMed: 2202881]
83. Rietschel P, et al. Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. *CID*. 2000; 31:1240–1244.
84. Wunder DM, et al. Hypogonadism in HIV-1-infected men is common and does not resolve during antiretroviral therapy. *Antivir Ther*. 2007; 12:261–265. [PubMed: 17503668]
85. Bhasin S, et al. Effects of testosterone supplementation on whole body and regional fat mass and distribution in human immunodeficiency virus-infected men with abdominal obesity. *J Clin Endocrinol Metab*. 2007; 92:1049–1057. [PubMed: 17164307]
86. Schambelan M, et al. Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial Serostim Study Group. *Ann Intern Med*. 1996; 125:873–882. [PubMed: 8967667]
87. Kotler DP, et al. Effects of growth hormone on abnormal visceral adipose tissue accumulation and dyslipidemia in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2004; 35:239–252. [PubMed: 15076238]
88. Kotler DP, et al. Effects of growth hormone on visceral adipose tissue and dyslipidemia in HIV, an erratum. *J Acquir Immune Defic Syndr*. 2006; 43:378–380. [PubMed: 17079997]
89. Luzi L, et al. GH treatment reduces trunkal adiposity in HIV-infected patients with lipodystrophy: a randomized placebo-controlled study. *Eur J Endocrinol*. 2005; 153:781–789. [PubMed: 16322383]
90. Hansen BR, et al. Long-term high-physiological-dose growth hormone reduces intra-abdominal fat in HIV-infected patients with a neutral effect on glucose metabolism. *HIV Med*. 2010; 11:266–275. [PubMed: 20002779]
91. Lo J, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *JAMA*. 2008; 300:509–519. [PubMed: 18677023]
92. Lo J, You SM, Liebau J, Lee H, Grinspoon S. Effects of low-dose growth hormone withdrawal in patients with HIV. *JAMA*. 2010; 304:272–274. [PubMed: 20639560]

93. Falutz J, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med*. 2007; 357:2359–2370. [PubMed: 18057338]
94. Falutz J, et al. Effects of tesamorelin, a growth hormone-releasing factor, in HIV-infected patients with abdominal fat accumulation: a randomized placebo-controlled trial with a safety extension. *JAIDS*. 2010; 53:311–322. [PubMed: 20101189]
95. Falutz J, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *J Clin Endocrinol Metab*. 2010; 95:4291–4304. [PubMed: 20554713]
96. Renehan AG, et al. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet*. 2004; 363:1346–1353. [PubMed: 15110491]
97. Clayton PE, Banerjee I, Murray PG, Renehan AG. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nat Rev Endocrinol*. 2011; 7:11–24. [PubMed: 20956999]
98. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. 2007; 370:59–67. [PubMed: 17617273]
99. Grunfeld C, et al. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab*. 1992; 74:1045–1052. [PubMed: 1373735]
100. Feingold KR, et al. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. *J Clin Endocrinol Metab*. 1993; 76:1423–1427. [PubMed: 8501146]
101. Tien PC, et al. HIV, HAART, and lipoprotein particle concentrations in the Women's Interagency HIV Study. *AIDS*. 2010; 24:2809–2817. [PubMed: 20871387]
102. Baker J, et al. High-density lipoprotein particles and markers of inflammation and thrombotic activity in patients with untreated HIV infection. *J Infect Dis*. 2010; 201:285–292. [PubMed: 19954384]
103. Riddler SA, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003; 289:2978–2982. [PubMed: 12799406]
104. Shafran SD, Mashinter LD, Roberts SE. The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. *HIV Med*. 2005; 6:421–425. [PubMed: 16268824]
105. Lee GA, et al. The metabolic effects of lopinavir/ritonavir in HIV-negative men. *AIDS*. 2004; 18:641–649. [PubMed: 15090769]
106. Shikuma CM, et al. Metabolic effects of protease inhibitor-sparing antiretroviral regimens given as initial treatment of HIV-1 Infection (AIDS Clinical Trials Group Study A5095). *J Acquir Immune Defic Syndr*. 2007; 44:540–550. [PubMed: 17245230]
107. van Leth F, et al. Nevirapine and Efavirenz Elicit Different Changes in Lipid Profiles in Antiretroviral- Therapy-Naive Patients Infected with HIV-1. *Plos Med*. 2004; 1:e19. [PubMed: 15526045]
108. Tungsiripat M, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *AIDS*. 2010; 24:1781–1784. [PubMed: 20495438]
109. Dube MP, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2003; 37:613–627. [PubMed: 12942391]
110. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001; 285:2486–2497. [PubMed: 11368702]
111. Law MG, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med*. 2006; 7:218–230. [PubMed: 16630034]

112. Friis-Moller N, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil.* 2010; 17:491–501. [PubMed: 20543702]
113. Gatell J, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. *Clin Infect Dis.* 2007; 44:1484–1492. [PubMed: 17479947]
114. Parienti JJ, Massari V, Rey D, Poubeau P, Verdon R. Efavirenz to nevirapine switch in HIV-1-infected patients with dyslipidemia: a randomized, controlled study. *CID.* 2007; 45:263–266.
115. Eron JJ, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet.* 2010; 375:396–407. [PubMed: 20074791]
116. Martinez E, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS.* 2010; 24:1697–1707. [PubMed: 20467288]
117. Fisac C, et al. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine. *AIDS.* 2005; 19:917–925. [PubMed: 15905672]
118. Calza L, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. *AIDS.* 2005; 19:1051–1058. [PubMed: 15958836]
119. Silverberg MJ, et al. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. *annals.* 2009; 150:301–313.
120. Aberg JA, et al. A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. *AIDS Res Hum Retroviruses.* 2005; 21:757–767. [PubMed: 16218799]
121. Dube MP, et al. Safety and efficacy of extended-release niacin for the treatment of dyslipidaemia in patients with HIV infection: AIDS Clinical Trials Group Study A5148. *Antivir Ther.* 2006; 11:1081–1089. [PubMed: 17302378]
122. Gerber JG, et al. Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: results of ACTG A5186. *J Acquir Immune Defic Syndr.* 2008; 47:459–466. [PubMed: 17971707]
123. Gerber MT, et al. Niacin in HIV-infected individuals with hyperlipidemia receiving potent antiretroviral therapy. *Clin Infect Dis.* 2004; 39:419–425. [PubMed: 15307011]
124. Wohl DA, et al. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counseling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. *Clin Infect Dis.* 2005; 41:1498–1504. [PubMed: 16231263]
125. Miller J, et al. A randomized, double-blind study of gemfibrozil for the treatment of protease inhibitor-associated hypertriglyceridaemia. *AIDS.* 2002; 16:2195–2200. [PubMed: 12409741]
126. Aslangul E, et al. Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial. *AIDS.* 2010; 24:77–83. [PubMed: 19838098]
127. Moyle GJ, et al. Dietary advice with or without pravastatin for the management of hypercholesterolaemia associated with protease inhibitor therapy. *AIDS.* 2001; 15:1503–1508. [PubMed: 11504982]
128. Henry K, Melroe H, Huebsch J, Hermundson J, Simpson J. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet.* 1998; 352:1031–1032. [PubMed: 9759748]
129. Fichtenbaum CJ, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS.* 2002; 16:569–577. [PubMed: 11873000]
130. Sekar, VJ.; Spinosa-Guzman, S.; Marien, K., et al. Pharmacokinetic drug-drug interaction between the new HIV protease inhibitor darunavir (TMC114) and the lipid-lowering agent pravastatin [abstr 55]. Program and Abstracts of the 8th International Workshop on Pharmacology of HIV Therapy; Budapest, Hungary. Apr 16–18, 2007;
131. Darunavir (Prezista) prescribing information. Raritan, NJ: Tibotec, Inc; 2009 Jun. (package insert)

132. Kiser JJ, et al. Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *JAIDS*. 2008; 47:570–578. [PubMed: 18176327]
133. Hsyu PH, Schultz-Smith MD, Lillibridge JH, Lewis RH, Kerr BM. Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother*. 2001; 45:3445–3450. [PubMed: 11709322]
134. Gerber JG, et al. Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS clinical trials group 5108 study. *J Acquir Immune Defic Syndr*. 2005; 39:307–312. [PubMed: 15980690]
135. Brown TT, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. 2005; 165:1179–1184. [PubMed: 15911733]
136. Bastard JP, et al. High incidence and risk factors for diabetes over 9-year follow-up after first generation protease inhibitor initiation in the ARNS CO8 APROCO-COPILOTE cohort. *Antiviral Therapy*. 2009; 14 (Suppl 2):A5.
137. Grunfeld C. Insulin resistance in HIV infection: drugs, host responses, or restoration to health? *Top HIV Med*. 2008; 16:89–93. [PubMed: 18591716]
138. Blumer RM, et al. Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. *AIDS*. 2008; 22:227–236. [PubMed: 18097225]
139. Fleischman A, et al. Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults. *Am J Physiol Endocrinol Metab*. 2007; 292:E1666–E1673. [PubMed: 17284576]
140. Brown TT, et al. Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the Multicenter AIDS Cohort Study. *AIDS*. 2005; 19:1375–1383. [PubMed: 16103768]
141. Brown TT, Tassiopoulos K, Bosch RJ, Shikuma C, McComsey GA. Association between systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy. *Diabetes Care*. 2010; 33:2244–2249. [PubMed: 20664016]
142. Schambelan M, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *JAIDS*. 2002; 31:257–275. [PubMed: 12439201]
143. Wohl DA, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. 2006; 43:645–653. [PubMed: 16886161]
144. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2011; 34:S62–S69. [PubMed: 21193628]
145. Diop ME, et al. Inappropriately low glycosylated hemoglobin values and hemolysis in HIV-infected patients. *AIDS Res Hum Retroviruses*. 2006; 22:1242–1247. [PubMed: 17209766]
146. Kim PS, et al. Hemoglobin A1c Underestimates Glycemia in HIV Infection. *Diabetes Care*. 2009
147. Glesby MJ, et al. Glycated haemoglobin in diabetic women with and without HIV infection: data from the Women's Interagency HIV Study. *Antivir Ther*. 2010; 15:571–577. [PubMed: 20587850]
148. Fitch KV, et al. Effects of a lifestyle modification program in HIV-infected patients with the metabolic syndrome. *AIDS*. 2006; 20:1843–1850. [PubMed: 16954725]
149. Hadigan C, Rabe J, Grinspoon S. Sustained benefits of metformin therapy on markers of cardiovascular risk in human immunodeficiency virus-infected patients with fat redistribution and insulin resistance. *J Clin Endocrinol Metab*. 2002; 87:4611–4615. [PubMed: 12364443]
150. Derosa G. Efficacy and tolerability of pioglitazone in patients with type 2 diabetes mellitus: comparison with other oral antihyperglycaemic agents. *Drugs*. 2010; 70:1945–1961. [PubMed: 20883052]
151. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. 2006; 20:2165–2174. [PubMed: 17086056]
152. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab*. 2008; 93:3499–3504. [PubMed: 18593764]

153. Nathan DM, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*. 2007; 30:753–759. [PubMed: 17327355]
154. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007; 92:2506–2512. [PubMed: 17456578]
155. Worm SW, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010; 201:318–330. [PubMed: 20039804]
156. Triant VA, Meigs JB, Grinspoon SK. Association of C-reactive protein and HIV infection with acute myocardial infarction. *J Acquir Immune Defic Syndr*. 2009; 51:268–273. [PubMed: 19387353]
157. Triant VA, et al. Association of Immunologic and Virologic Factors With Myocardial Infarction Rates in a US Healthcare System. *J Acquir Immune Defic Syndr*. 2010
158. Ribaud HJ, et al. No Risk of Myocardial Infarction Associated With Initial Antiretroviral Treatment Containing Abacavir: Short and Long-Term Results from ACTG A5001/ALLRT. *Clin Infect Dis*. 2011; 52:929–940. [PubMed: 21427402]
159. Costagliola D, Lang S, Mary-Krause M, Boccard F. Abacavir and cardiovascular risk: reviewing the evidence. *Curr HIV/AIDS Rep*. 2010; 7:127–133. [PubMed: 20521126]
160. Lichtenstein K, et al. Analysis of Cardiovascular Risk Factors in the HIV Outpatient Study Cohort. In the Program and Abstracts of the 13th Conference of Retroviruses and Opportunistic Infections. Feb 5.2006 735
161. Fuster M, et al. Smoking cessation in HIV patients: rate of success and associated factors. *HIV Med*. 2009; 10:614–619. [PubMed: 19659946]
162. Petoumenos K, et al. Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(*). *HIV Med*. 2011; 20:10–1293.10.1111/j.1468-1293.2010.00901.x
163. Seaberg EC, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS*. 2005; 19:953–960. [PubMed: 15905677]
164. Chobanian AV, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003; 42:1206–1252. [PubMed: 14656957]
165. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009; 150:396–404. [PubMed: 19293072]
166. Hunt PW, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis*. 2008; 197:126–133. [PubMed: 18171295]
167. French MA, King MS, Tschampa JM, da Silva BA, Landay AL. Serum immune activation markers are persistently increased in patients with HIV infection after 6 years of antiretroviral therapy despite suppression of viral replication and reconstitution of CD4+ T cells. *J Infect Dis*. 2009; 200:1212–1215. [PubMed: 19728788]
168. Shikuma CM, et al. Change in High-Sensitivity C-Reactive Protein (hsCRP) Levels Following Initiation of Efavirenz-Based Antiretroviral Regimens in HIV-Infected Individuals. *AIDS Res Hum Retroviruses*. 2010
169. Brenchley JM, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med*. 2006; 12:1365–1371. [PubMed: 17115046]
170. Deeks SG. Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy. *Top HIV Med*. 2009; 17:118–123. [PubMed: 19890183]

Key Points

- Subcutaneous lipoatrophy, central lipohypertrophy, dyslipidemia and insulin resistance are common among HIV-infected individuals and probably contribute to these patients' increased risk of type 2 diabetes mellitus and cardiovascular disease
- The cause of these disorders is multifactorial and includes the effects of chronic HIV infection, direct and indirect toxicity of highly active antiretroviral therapy (HAART), and demographic, behavioral and genetic susceptibility factors
- Aggressive treatment of modifiable cardiovascular risk factors is warranted, but interactions between HAART and medications to treat metabolic disease, such as certain statin medications, should also be considered
- A new medication for the treatment of central lipohypertrophy is now available, tesamorelin, but more work is needed to understand the long-term benefits and risks
- Chronic inflammation in HIV-infected individuals probably has an important role in the pathogenesis of these patients' metabolic disease, but further investigation of this effect and effective intervention strategies are required

Figure 1.

45-year-old HIV-infected woman with a) moderate to severe facial lipoatrophy with marked adipose tissue wasting in the malar areas with extension of adipose tissue wasting to buccal and temporal areas, and b) central lipohypertrophy with a large dorso-cervical fat pad.

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Figure 2.

A 58-year-old HIV-infected man with severe visceral abdominal fat accumulation, umbilical hernia and diffuse subcutaneous lipoatrophy including loss of subcutaneous abdominal adipose tissue with resultant prominent appearance of veins.

Table 1

Treatment strategies for adipose tissue changes in HIV-infected individuals

Strategy	Effect				Comments
	No effect	Modest effect	Clinically significant effect	Unclear	
Lipoatrophy					
Switching antiretroviral therapy		X			Switching from stavudine or zidovudine to abacavir or tenfovir disoproxil fumarate; best available strategy for lipoatrophy
Thiazolidinediones		X			Effect not clinically significant; availability of rosiglitazone limited due to increased risk of cardiovascular disease; pioglitazone associated with decreased levels of triglycerides, increased levels of HDL cholesterol, slight increased levels of LDL cholesterol
Pravastatin	X				
Uridine	X				
Facial fillers			X		Potential adverse effects include fat hypertrophy with autotransplantation, skin nodules with resorbable fillers and local infections with permanent fillers
Leptin				X	No effect on peripheral adipose tissue, but may improve insulin resistance and dyslipidemia
Lipohypertrophy					
Switching antiretroviral therapy	X				Overall, no benefit except for switching from lopinavir plus ritonavir to atazanavir plus ritonavir in one small study
Lifestyle changes		X			
Metformin		X			May worsen lipoatrophy
Growth hormone			X		Rejected by FDA because of safety concerns
Tesamorelin			X		FDA approved 2010; long-term benefits and risks unclear
Liposuction (dorsocervical fat pad)			X		Can re-accumulate

Table 2

Safety of co-administration of protease inhibitors and medications to treat lipid and glucose abnormalities

Medication	Safety with protease inhibitors co-administration			Comments
	Not Safe	Use with caution	Safe	
Lipid lowering medications				
Pravastatin			X	Exception: should not be used with darunavir
Fluvastatin			X	
Atorvastatin		X		
Rosuvastatin		X		
Simvastatin	X			
Lovastatin	X			
Niacin			X	
Fenofibrate			X	
Gemfibrozil			X	
Omega-3 fatty acids			X	
Medications for type 2 diabetes mellitus				
Metformin			X	
Sulfonylureas			X	
Pioglitazone			X	
Acarbose			X	
Exenatide			X	
Liraglutide			X	
Sitagliptin			X	
Saxagliptin		X		
Insulin			X	