Body Composition and Metabolic Changes in HIV-Infected Patients

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As antiretroviral therapy has decreased human immunodeficiency virus (HIV)–associated mortality, cardiometabolic abnormalities have become increasingly apparent in HIV-infected individuals. Many patients treated for HIV infection exhibit body composition changes, including peripheral fat atrophy and visceral lipohypertrophy. In addition, HIV-infected individuals demonstrate a higher prevalence of dyslipidemia, insulin resistance and diabetes, and cardiovascular risk, compared with the general population. Although antiretroviral therapy appears to contribute to some of the cardiometabolic abnormalities in HIV infection, HIV itself, immunologic factors, and lifestyle factors are also important mediators of cardiovascular risk. Treatment strategies for body composition changes and cardiometabolic abnormalities in HIV infection include lifestyle modification, lipid-lowering agents, insulin sensitizers, and treatments to reverse endocrine abnormalities in HIV, including growth hormone–releasing hormone. None of these strategies has comprehensively addressed the abnormalities experienced by this population, however, and further research is needed into combined strategies to improve body composition and ameliorate cardiovascular risk.

A large percentage of individuals with human immunodeficiency virus (HIV) infection, particularly those receiving antiretroviral therapy, experience peripheral fat atrophy, visceral fat accumulation, and cardiometabolic comorbidities, including dyslipidemia, impaired glucose homeostasis, and increased risk for cardiovascular disease. As antiretroviral therapy continues to increase life expectancy for HIV-infected individuals, management of these issues becomes increasingly important. This review will describe changes in body composition, lipid profile, glucose homeostasis, and cardiovascular health in individuals with HIV infection, concluding with a review of existing strategies and research goals to address these issues.

PERIPHERAL LIPOATROPHY AND VISCERAL ADIPOSE TISSUE ACCUMULATION IN HIV INFECTION

Abnormal fat distribution occurs in more than half of HIV-infected patients treated with antiretroviral therapy [1, 2]. Patients may experience lipoatrophy in the face and limbs; lipohypertrophy of visceral, breast, cervical, and/or dorsocervical adipose tissue; or a combination of lipoatrophy and lipohypertrophy. In addition to lipohypertrophy of existing fat depots, HIV-infected individuals also exhibit increased prevalence of ectopic fat distribution in the liver, muscles, and dorsocervical area [3–5]. Although certain antiretroviral medications appear more highly associated with abnormalities in fat redistribution than others [6], changes in body composition may occur to some degree with any antiretroviral strategy. Studies of antiretroviral-naive patients beginning treatment show clear increases in visceral adipose tissue and trunk fat (Figure 1) even with contemporary regimens (Supplementary Figure 1) [7, 8].

Decreases in limb subcutaneous fat are also prevalent in regimens including many antiretrovirals, including zidovudine and stavudine (Figure 1) [7], whereas in
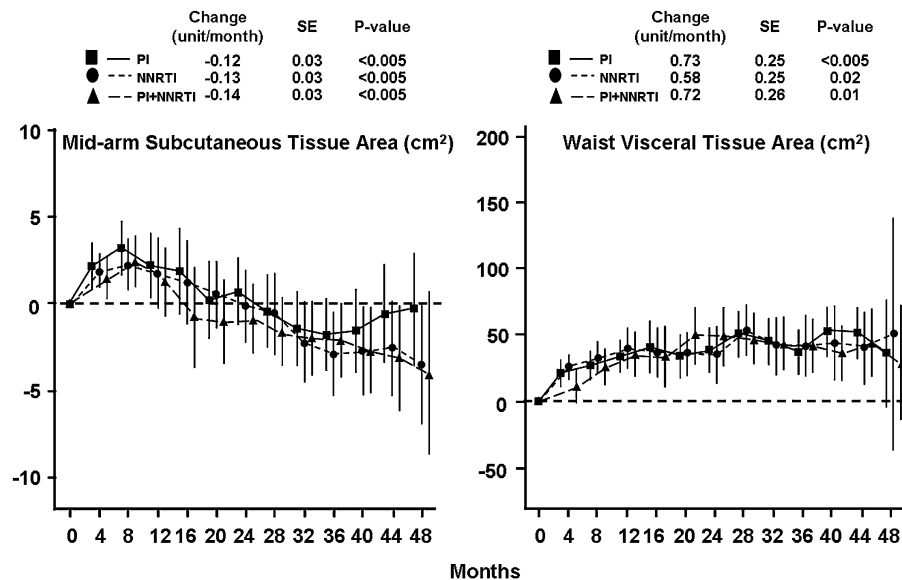
		Change (unit/month)	SE	P-value
■ —	PI	-0.12	0.03	<0.005
● ---	NNRTI	-0.13	0.03	<0.005
▲ – –	PI+NNRTI	-0.14	0.03	<0.005

		Change (unit/month)	SE	P-value
■ —	PI	0.73	0.25	<0.005
● ---	NNRTI	0.58	0.25	0.02
▲ – –	PI+NNRTI	0.72	0.26	0.01

Figure 1. Changes in mid-arm subcutaneous fat and visceral adipose tissue area in antiretroviral-naive patients beginning treatment with regimens involving protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), or PIs plus NNRTIs. Mean change from baseline and 95% confidence intervals are shown. For each strategy, the rates of change beginning at the 4-month follow-up visit are shown at the top of each panel, with *P* values for comparison to the null hypothesis. Adapted from [7] by permission of Lippincott Williams & Wilkins, Inc.

patients who are using newer agents such as abacavir, lamivudine, tenofovir, efavirenz, and atazanavir, lipoatrophy may be less common and limb fat may instead increase (Supplementary Figure 1) [8]. The mechanisms of lipoatrophy are numerous and include the inhibition of adipocyte differentiation by protease inhibitors [9, 10] and the impairment of mitochondrial function by nucleoside reverse-transcriptase inhibitors, particularly thymidine analogues [11, 12]. The etiology of lipohypertrophy and ectopic fat accumulation is less clear. The phenotypic similarity of HIV-associated lipohypertrophy and Cushing syndrome has prompted detailed investigation of cortisol dynamics. Although a minority of individuals with HIV-associated lipohypertrophy have demonstrated elevated serum and urine cortisol concentrations, HIV-infected lipodystrophic individuals show appropriate suppression of cortisol levels in response to dexamethasone and also demonstrate normal diurnal variation in cortisol levels, arguing against true Cushing syndrome [13, 14]. Rather, lipohypertrophy may be related to elevated levels of inflammatory cytokines [15] or to "overflow" storage of surplus energy, particularly triglyceride and free fatty acid, that cannot be stored in atrophic subcutaneous depots [16]. Lipohypertrophy does not always occur in conjunction with lipoatrophy, however, and further research is necessary to determine the etiology of abnormal fat accumulation during HIV infection.

Although HIV-infected individuals with abnormal fat distribution generally maintain a body mass index in the normal or overweight range, they often experience cardiometabolic complications similar to those seen in frank obesity. Hadigan et al [17] demonstrated significantly increased prevalence of dyslipidemia and impaired glucose homeostasis in HIV-infected individuals with abnormal fat distribution, compared with HIV-negative controls matched for age and body mass index. Samaras et al [18] recently demonstrated that HIV-infected men with lipodystrophy had levels of C-reactive protein, adiponectin, tumor necrosis factor α, and interleukin 6 similar to those in obese HIV-negative men, despite significantly lower body mass index and body fat. Both peripheral fat atrophy and visceral fat accumulation are associated with an increase in cardiometabolic risk factors. Wohl et al [19] have shown that both increased visceral fat and decreased subcutaneous leg fat are associated with elevated triglyceride levels (Supplementary Figure 2) and decreased high-density lipoprotein cholesterol (HDL-C) levels. Likewise, both decreased subcutaneous leg fat and increased visceral fat are strongly associated with decreased insulin sensitivity in this population [20, 21], as well as in the general population [22]. Albu et al [21] demonstrated that insulin sensitivity increases in proportion to the percentage of total body fat stored in the lower extremities in both HIV-infected and noninfected women. In the Fat Redistribution and Metabolic Change in HIV (FRAM) cohort, HIV-infected individuals in the highest tertiles of upper trunk subcutaneous adipose tissue and visceral adipose tissue had a significantly increased risk of insulin resistance (odds

ratios, 2.1 for upper trunk subcutaneous adipose tissue and 3.1 for visceral adipose tissue), compared with those in the lowest tertiles [20]. Data from FRAM also have demonstrated that both peripheral lipoatrophy and visceral lipohypertrophy are associated with increased Framingham Risk Score, which is predictive of myocardial infarction, in HIV-infected individuals [23]. Scherzer et al [24] have recently shown an association between visceral adiposity and overall mortality in individuals with HIV infection, such that individuals in the highest tertile of visceral adipose tissue had an odds ratio of mortality of 2.1, compared with those in the lowest tertile. Importantly, both lipoatrophy and visceral fat accumulation are associated with subclinical atherosclerosis as measured by coronary artery calcium score from computed tomography angiography [25], and visceral fat is associated with progression of subclinical atherosclerosis in HIV-infected patients [26].

INSULIN RESISTANCE AND DIABETES MELLITUS IN HIV INFECTION

Although antiretroviral-naive individuals appear to have a risk of diabetes that is similar to [27, 28] or modestly greater than [29] that for the general population, individuals treated with antiretroviral therapy show a marked increase in impaired glucose tolerance and type 2 diabetes mellitus [17, 29]. In a cohort of HIV-infected individuals with abnormal fat distribution, Hadigan et al [17] demonstrated that approximately one-third of patients had abnormal glucose tolerance and that 7% had previously undiagnosed diabetes, according to a 2-hour glucose following oral glucose tolerance test. More recently, Brown et al [29] demonstrated that HIV-infected men receiving antiretroviral therapy had a baseline prevalence of diabetes of 14%, compared with 5% in controls, and had an approximately 4-fold risk of developing diabetes during follow-up.

One of the primary contributors to impaired glucose homeostasis in the HIV-infected population is abnormal fat distribution, particularly visceral adiposity and lower extremity fat atrophy. Intramyocellular lipid levels, which are generally increased in HIV-infected patients compared with those in controls, are also strongly associated with insulin resistance [3]. In addition, numerous other factors also appear to play important roles in the high prevalence of insulin resistance and diabetes in this population. Brown et al [30] have demonstrated that systemic inflammatory markers, including high sensitivity c-reactive protein and tumor necrosis factor receptors 1 and 2, are associated with increased risk of developing diabetes in HIV infection, suggesting a role of chronic inflammation in impaired glucose metabolism. In support of this, protease inhibitors are known to induce suppressor of cytokine signaling 1, which upregulates

tumor necrosis factor α and other inflammatory cytokines [31]. Antiretrovirals also appear to contribute to an increased risk of diabetes. In the Data Collection on Adverse Events of Anti-HIV Drugs (D.A.D.) study, the incidence of diabetes increased with increasing cumulative exposure to antiretrovirals, even after control for other risk factors [32]. Moreover, Capeau et al [33] recently demonstrated that the incidence of diabetes may be related more specifically to the use of indinavir, stavudine, and didanosine, as well as to increased waist-to-hip ratio and peripheral lipoatrophy, and it may be decreasing with the use of newer, more contemporary agents. The mechanisms by which antiretrovirals may impair glucose homeostasis are numerous. Many protease inhibitors block the glucose transporter GLUT4, impairing insulin-stimulated glucose use [34]. Protease inhibitors also appear to directly affect glucose sensing by β cells, causing impaired insulin release [35]. Nucleoside reverse-transcriptase inhibitors, particularly the thymidine-containing analogues stavudine and zidovudine, may also contribute to insulin resistance through adverse effects on mitochondria [12, 36]. Fleischman et al [36] have demonstrated that administration of stavudine to non-HIV–infected healthy controls for 1 month significantly reduced insulin sensitivity and decreased mitochondrial DNA levels, compared with placebo administration. Finally, hepatitis C virus coinfection may be associated with a higher risk of diabetes in HIV-infected individuals [28].

DYSLIPIDEMIA IN HIV INFECTION

Early in the course of untreated HIV infection, both HDL-C and low-density lipoprotein cholesterol (LDL-C) levels decrease and triglyceride levels increase [37, 38]. Following treatment with antiretroviral therapy, triglyceride levels often increase further [39], and HDL-C levels typically remain low. LDL-C levels commonly increase, often beyond the baseline level before HIV acquisition [37]. Thus, many patients with HIV infection, particularly those with associated body composition abnormalities, have a dyslipidemic profile of decreased HDL-C and increased triglyceride and LDL-C levels [17]. An increased triglyceride level is often the most pronounced lipid abnormality in HIV-infected patients and appears to contribute independently to increased cardiovascular risk in this population. In the D.A.D. study, each 2-fold increase in triglyceride levels was associated with a 17% increase in the risk of myocardial infarction (relative risk, 1.17; 95% confidence interval 1.06–1.29), after control for other traditional risk factors [40]. Moreover, Janiszewski et al [41] reported that, in a cohort of >2000 men and women with HIV infection, hypertriglyceridemia, together with increased waist circumference, was highly predictive of metabolic syndrome, insulin resistance, and cardiovascular risk as measured by the Framingham Risk Score. In addition to

abnormal levels of HDL-C, triglycerides, and LDL-C, Riddler et al [42] have also demonstrated that HIV-infected individuals receiving antiretroviral therapy have altered particle size, compared with HIV-negative controls, with increased amounts of very low-density lipoprotein cholesterol and small LDL-C particles and decreased amounts of HDL-C and large LDL-C particles [42]. These abnormalities were not seen in antiretroviral-naive individuals with HIV infection, who exhibited a low HDL-C level but also a decreased number of small LDL-C particles, compared with controls [42].

Both increased visceral fat and decreased subcutaneous adipose tissue are associated with increased circulating free fatty acid and elevated triglyceride levels [19, 43]. In addition, detailed studies of lipid handling during HIV infection have shown a number of abnormalities. Rates of basal lipolysis are significantly higher in HIV-infected individuals, compared with uninfected controls [43, 44]. Moreover, HIV-infected individuals demonstrate a significantly higher free fatty acid level following an oral glucose challenge, reflecting reduced ability of insulin to suppress lipolysis at the level of the adipocyte [43]. Hepatic de novo lipogenesis is also increased [45], and peripheral fatty acid trapping is impaired [46]. Together, these abnormalities lead to increased circulating free fatty acid, very low-density lipoprotein cholesterol, and triglyceride levels. The etiology of these abnormalities appears in part to be due to HIV infection itself, as changes in lipid handling are seen in individuals naive to antiretroviral therapy, potentially in relation to elevated levels of circulating inflammatory cytokines, particularly interferon α [45]. In addition, HIV-infected individuals may have increased saturated fat intake compared with controls, exacerbating lipid abnormalities [47]. Antiretrovirals, particularly protease inhibitors, also contribute to impaired lipid handling. Many protease inhibitors impair adipocyte differentiation and decrease triglyceride accumulation in adipocytes, leading to increased circulating triglyceride levels [9, 48]. In addition, a common protease inhibitor, ritonavir, has been shown to increase basal lipolysis in vitro [49], and ritonavir-boosted lopinavir, darunavir, and atazanavir decrease fatty acid oxidation in skeletal muscle cells in vitro [50]. Both of these effects, if consistent in vivo, would increase circulating free fatty acid levels. Different protease inhibitors have varying effects on lipid handling, with atazanavir typically showing less effect on adipocyte differentiation, triglyceride storage, and fatty acid oxidation than other protease inhibitors, such as lopinavir or ritonavir [9, 50].

TREATMENT STRATEGIES TO AMELIORATE CARDIOMETABOLIC RISK IN HIV-INFECTED INDIVIDUALS

Since HIV-infected individuals demonstrate multiple cardiovascular risk factors, including central adiposity, insulin resistance,

dyslipidemia, and increased systemic inflammation, a comprehensive strategy will likely be necessary to address cardiometabolic risk in this population.

Overall Cardiometabolic Risk

Lifestyle modification should be the first-line approach, with a focus on smoking cessation in addition to exercise and diet modification. Formalized exercise programs in individuals with HIV infection have demonstrated benefit to reduce cholesterol and triglyceride levels [51, 52] and decrease waist circumference [51, 53]. In addition, Fitch et al demonstrated reductions in systolic blood pressure and hemoglobin A1c (HbA1c) level with a 6-month lifestyle intervention modeled after the National Cholesterol Education Project (NCEP) recommendations for diet and activity [53].

In many patients, however, lifestyle modification may not be adequate to thoroughly address cardiovascular risk, and in such patients more specific strategies to reduce insulin resistance, dyslipidemia, and central fat accumulation may be useful.

Insulin Resistance

Metformin treatment in patients with central fat accumulation has been shown to significantly improve insulin levels, waist circumference, and diastolic blood pressure [54], as well as tissue plasminogen activator antigen and plasminogen activator inhibitor 1 levels [55]. A recent study suggests metformin may reduce coronary artery calcium progression in HIV-infected patients with the metabolic syndrome [56]. Importantly, however, metformin appears to decrease both visceral and subcutaneous adipose tissue and may not be appropriate for individuals with severe lipoatrophy [54]. In contrast, thiazolidinediones, particularly pioglitazone, may increase limb fat while also improving insulin sensitivity and increasing HDL-C levels [57, 58]. Of interest, a recent pilot study involving HIV-infected men with lipoatrophy used a combination of pioglitazone and leptin, demonstrating that the addition of leptin further decreased insulin resistance, increased adiponectin levels, and decreased postprandial glucose levels, compared with pioglitazone alone [59]. Leptin is an investigational drug, and further study is needed regarding its effects in HIV-associated body composition changes. Addition of exercise training to pioglitazone therapy also augments the effects of pioglitazone in reducing insulin resistance [60]. Rosiglitazone has also been studied in this population, but effects on limb fat are not consistent, and rosiglitazone may have adverse cardiovascular effects [58, 61, 62].

Dyslipidemia

For individuals with dyslipidemia, both statin and fibrate therapy have shown a benefit [63–65]. Statins may be slightly less effective in HIV-infected patients than in the general
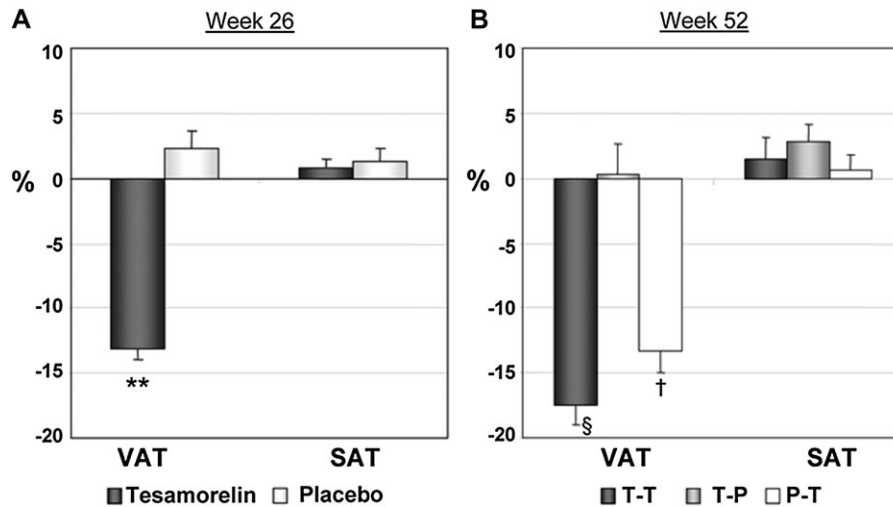
Figure 2. Percentage change from baseline in abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) at 26 weeks (a) and 52 weeks (b). Data are mean ± standard error of the mean. T-T indicates the group receiving tesamorelin for 52 weeks. T-P indicates the group receiving tesamorelin from week 0–26 followed by placebo from week 27–52. P-T indicates the group receiving placebo from week 0–26 followed by tesamorelin from week 27–52. **, $P < .001$ vs placebo; §, $P < .001$ vs baseline and vs T-P; †, $P < .001$ vs baseline. From Falutz et al [83]. Copyright 2010, The Endocrine Society.

population but have demonstrated a reduction of approximately 25% in LDL-C levels [64]. Doses may need to be reduced because of interactions with many protease inhibitors, which are metabolized by CYP3A4 and may increase serum concentrations of certain statins [66]. In patients with elevated triglyceride levels, both gemfibrozil [64, 67] and fenofibrate [68, 69] lower triglyceride levels significantly, although gemfibrozil appears to be somewhat less effective in HIV-infected individuals, compared with non–HIV-infected individuals. For individuals with elevations in both triglyceride and LDL-C levels, combination therapy with fibrates and statins is effective [69]. Niacin and fish oil have also been investigated in the HIV-infected population. Wohl et al [70] demonstrated that fish oil lowers triglyceride levels by 20%–25% and is well tolerated in HIV-infected individuals receiving antiretroviral therapy. Niacin, alone or in combination with a fibrate, also effectively reduces triglyceride levels and may have favorable effects on HDL-C levels, as well [68, 71, 72]. In addition, niacin may improve endothelial function [73] and increase adiponectin levels [68]. Niacin may have adverse effects on glycemia [68, 72], however, and may not be appropriate for patients with impaired glucose homeostasis. The effects of niacin, particularly the extended-release formulation, on insulin resistance may be transient [71], and the long-term effects of extended-release niacin on glucose homoeostasis remain under investigation. Finally, acipimox has also been investigated and demonstrates both reduction in triglyceride levels and improved insulin sensitivity, but acipimox remains investigational in the United States [74].

Central Fat Accumulation

A number of agents have been proposed to reduce central fat accumulation. Both lifestyle modification and metformin have been shown to reduce waist circumference in HIV-infected patients, but they are not selective in this regard, and they tend to cause weight loss and reduce subcutaneous and visceral fat. Growth hormone secretion is reduced in HIV-infected individuals in association with increased visceral adiposity [75, 76], and both exogenous growth hormone and growth hormone–releasing hormone effectively reduce visceral fat and decrease triglyceride levels in HIV-infected individuals [77–80]. Exogenous growth hormone per se, as distinct from growth hormone–releasing hormone, the antecedent secretagogue hormone, exacerbates insulin resistance [79, 80], however, and thus remains investigational in this population predisposed to insulin resistance at baseline. A growth hormone–releasing hormone analogue, tesamorelin, was recently approved by the US Food and Drug Administration to reduce visceral fat in HIV-infected individuals with increased central fat accumulation. This strategy is known to increase endogenous growth hormone pulsatility [81] and may thus be a more rational and better tolerated strategy than use of exogenous growth hormone, which increases growth hormone levels in a nonpulsatile fashion. Indeed, treatment for 26–52 weeks with tesamorelin effectively reduces visceral adiposity by approximately 15% without significantly affecting subcutaneous adiposity in HIV-infected patients (Figure 2) [82, 83]. In addition, tesamorelin significantly reduced triglyceride levels by approximately 40 mg/dL over 6 months

Table 1. Summary of Treatment Strategies for Human Immunodeficiency Virus–Associated Cardiometabolic Abnormalities

Variable	Lifestyle	Metformin	TZD	Lipid-Lowering Agents	GHRH Analogue
Lipid levels	May improve	No effect	May increase HDL-C level	Improve	Improve
Glucose homeostasis	Improves	Improves	Improves	No effect	Minimal effect[a]
Central obesity	Improves	May improve	No effect	No effect	Improves
Peripheral lipoatrophy	No effect	May Worsen	May Improve	No effect	No effect
Safety	Excellent	Good	Fair	Good	Good

Abbreviations: GHRH, growth hormone–releasing hormone; HDL-C, high-density lipoprotein cholesterol; TZD, thiazolidinedione.

[a] GHRH analogue therapy may modestly increase hemoglobin A1c levels over 6 months of treatment but shows no effect over 12 months.

and did not affect fasting glucose or insulin levels or results of 2-hour glucose or insulin following oral glucose tolerance testing [83]. Tesamorelin did have a modest effect on HbA1c levels, with an increase of 0.1% ± 0.4% over 6 months, but there was no effect on HbA1c levels after 52 weeks of treatment, potentially because the beneficial effects of visceral fat reduction counterbalanced any hyperglycemic effects of tesamorelin [83]. In association with decreases in visceral fat, tesamorelin also has beneficial effects to increase levels of adiponectin, an adipokine associated with increased insulin sensitivity, and to reduce tissue plasminogen activator antigen levels, which appear to be associated with increased cardiovascular risk [84]. Further research is needed to determine whether reductions in visceral fat with tesamorelin may be associated with other cardiometabolic benefits. Finally, tesamorelin improved psychological distress related to abdominal fat accumulation and may thus increase well-being and quality of life.

Overall, tesamorelin was well tolerated, but 3% of people who received it had local and distant hypersensitivity reactions requiring discontinuation of the drug. Moreover, the effect of tesamorelin did not last beyond treatment, with reaccumulation of visceral fat occurring within 3–6 months of discontinuation, and the optimal duration of treatment remains unknown. Patients receiving tesamorelin should be carefully monitored to ensure that IGF-I levels remain within the normal range, as supraphysiologic levels of IGF-I may cause side effects, and there is concern that, in theory, increased IGF-I levels may be associated with malignancy.

In summary, treatment of HIV-associated cardiometabolic and body composition abnormalities requires a comprehensive approach, including lifestyle modification, smoking cessation, and use of lipid-lowering and/or insulin sensitizing agents when appropriate (see Table 1). For patients with central adiposity, tesamorelin may beneficially augment endogenous growth hormone secretion, selectively reducing visceral fat and lowering triglyceride levels. These currently available agents do not completely reverse the cardiometabolic abnormalities in many patients, however, and further research is needed into novel and combination agents to address cardiovascular and metabolic risk in this population.

Supplementary Data

Notes

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Additional cited references are available online as supplementary material.