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Review

Treatment Options for HIV-Associated Central Fat Accumulation

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Abstract

Central fat accumulation is increasingly recognized as a problem for patients with HIV infection. The term "lipodystrophy" has been used to describe collectively a constellation of body habitus changes and metabolic abnormalities commonly observed in HIV-infected patients, particularly since the advent of highly active antiretroviral therapy. Visceral fat accumulation can place patients at increased risk of coronary artery disease. Furthermore, body shape changes are a source of distress to patients that may compromise treatment adherence. Reduction of abdominal obesity can therefore be considered part of therapy in HIV-positive patients with visceral adipose tissue (VAT) accumulation. Currently, there are no drugs approved by the Food and Drug Administration for the treatment of HIV-associated central fat accumulation. Lifestyle modifications such as diet and exercise and switching antiretroviral therapies appear to be of limited value in reducing VAT. Metformin has shown some benefit in reducing VAT but at the expense of accelerating peripheral fat loss, and the thiazolidinediones have no effect on VAT. Similarly, testosterone does not appear to reduce VAT in these patients, and there are no data on anabolic steroids. Two large, randomized controlled trials have demonstrated the efficacy of recombinant human growth hormone (rhGH) in reducing visceral adipose tissue. There are also promising data regarding treatment with growth hormone releasing hormone (GHRH).

Introduction

A number of fat and metabolic abnormalities have been described in HIV-infected patients, especially those receiving highly active antiretroviral therapy (HAART). Early studies reported peripheral lipoatrophy[1] and central fat accumulation,[2] and the term "lipodystrophy syndrome" has been used to collectively describe the various disturbances of body composition (lipoatrophy, lipohypertrophy, or both) and metabolism (dyslipidemia, insulin resistance) observed in patients with HIV in the era of HAART. The changes in body habitus observed in HIV-infected patients were initially described as a "redistribution" syndrome,[3] which implied reciprocal loss of peripheral subcutaneous fat with accumulation of central fat. More recently, however, there has been increasing consensus that these are separate, although at times concurrent, phenomena.[4,5] Lipoatrophy is primarily subcutaneous fat loss. Fat deposition in patients with HIV occurs in the visceral depot (intra-abdominally), breasts, and/or dorsocervical area of the neck. Some patients have fat deposits in the form of lipomas. The term "HIV-associated adipose redistribution syndrome" (HARS) has been used to define a distinct subset of lipodystrophy that is primarily characterized by the abnormal accumulation of visceral adipose tissue (VAT), with or without comorbid lipoatrophy and/or metabolic abnormalities such as dyslipidemia or insulin resistance.[6–9] Aside from potential metabolic consequences, the presence of central lipohypertrophy has been shown to be significantly associated with poor body image and impaired quality of life in both men and women with HIV.[10,11] While there is increasing debate about the prevalence of central fat accumulation and its association with HAART,[4,12,13] few clinicians debate its existence in clinical practice. In the general population, accumulation of VAT carries a high risk of metabolic disturbance, including hyperlipidemia and insulin resistance.[14]

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This paper discusses the phenomenon of VAT in HIV patients and reviews the potential for cardiovascular sequelae of unchecked visceral adiposity. Currently, there are no drugs approved by the Food and Drug Administration for the treatment of HIV-associated central fat accumulation. However, a number of strategies, including lifestyle modification and drug therapies, have been investigated and this review provides an overview of potential treatment options.

Data for this review were identified by searches of MEDLINE and references from relevant articles. Search terms used were "HIV" and "metabolic disturbances or abnormalities," "fat or adipose accumulation," "lipohypertrophy," and "treatment." English-language articles were included. Preference was given to large-scale epidemiologic analyses and randomized controlled trials for treatment options.

Separating Central Fat Accumulation and Peripheral Lipoatrophy

Central or truncal fat consists of both subcutaneous adipose tissue (SAT) and VAT. We use the term central fat accumulation" (CFA) to describe abdominal adiposity in HIV patients where the specific fat depot is not defined or includes both visceral and subcutaneous compartments.

The fat abnormalities that occur in HIV-infected patients can involve an abnormal accumulation of VAT, sometimes associated with development of a dorsocervical fat pad ("buffalo hump") and/or lipoatrophy, which involves loss of subcutaneous fat, usually in the face, extremities and/or buttocks, but also sometimes in the trunk. Although CFA can coexist with peripheral lipoatrophy, data from cross-sectional and clinical trials suggest that these changes do not occur in tandem but rather as separate entities, each with a distinct pathogenesis and risk factors requiring different management strategies. However, studies into the longitudinal pattern of fat distribution in patients with HIV have been hampered by methodological problems and multiple potential confounders.

The cross-sectional Fat Redistribution and Metabolic Change in HIV Infection (FRAM) Study studied both men and women and examined fat changes based on concordance between the patient's report of a decrease or increase in fat over the previous 5 years and a researcher's determination that the patient had less or more fat at that site than normal healthy people.[4,12] Areas of truncal VAT and SAT were determined by magnetic resonance imaging (MRI). In FRAM, MRI measurements showed that HIV-infected men and women with clinical peripheral lipoatrophy had a smaller volume of adipose tissue in central sites compared with HIV-infected people without lipoatrophy.[4,12] There was no correlation between changes in central fat and peripheral fat in the cohort of HIV-infected men ($n = 425$), measured either by self-report or physical examination.[4] Moreover, the presence of peripheral lipoatrophy did not positively correlate with the presence of central lipohypertrophy (odds ratio [OR], 0.71; 95%, CI 0.47–1.06; $p = 0.10$) in men, but did correlate with the presence of central lipoatrophy (OR, 18.9; 95%, CI 5.7–63; $p < 0.0001$). In women, the presence of central lipohyertrophy was strongly correlated with a lower likelihood of peripheral lipoatrophy (OR, 0.39; 95%, CI 0.20–0.75; $p = 0.006$), and all women with central lipoatrophy also had peripheral lipoatrophy.[12] Because of the cross-sectional nature of this study, no definitive conclusions can be drawn about the dynamics of adipose tissue gains in visceral or subcutaneous compartments, but it is noteworthy that central adiposity was not correlated with SAT loss in the extremities, which argues for separate processes determining peripheral lipoatrophy and central lipohypertrophy.

Longitudinal data have added to the debate over the nature of central fat accumulation in HIV. The MultiCenter AIDS Cohort Study (MACS) showed that changes occurring over 4 years in waist circumference, a marker of central adiposity, did not differ between HIV-positive and HIV-negative subjects.[13] The Women's Interagency HIV study also found that the incidence of central lipohypertrophy, defined as patient self-report confirmed by waist circumference measurement during a 30-month period, was similar in HIV-positive women and HIV-negative controls.[15] To some extent, central fat accumulation occurring in patients with HIV might be confounded by changes typically seen with aging and in the context of the increasing prevalence of obesity in the general population. Further long-term prospective data are required to fully elucidate the natural history of central lipohypertrophy in patients with HIV.

There are limited clinical trial data examining the pattern of fat accumulation in patients with HIV after initiation of antiretroviral therapy. The recent AIDS Clinical Trials Group (ACTG) Study 384 evaluated 329 HIV-infected patients randomized to didanosine plus stavudine or zidovudine plus lamivudine plus nelfinavir, efavirenz, or both.[16] A substudy of 157 subjects who underwent dual-energy x-ray absorptiometry (DXA) scanning through week 64 supports the contention that CFA and peripheral lipoatrophy are independent processes.[16] However, because neither computed tomography (CT) scan nor MRI was used in this study, VAT area was not specifically quantified; truncal fat area included both subcutaneous and visceral fat. This study showed an increase in both trunk and limb fat during the first 16 weeks of treatment, and then a decline in limb fat from week 16–64, and a leveling off in trunk fat over the same time. By week 64, 36% of patients had developed increases in both trunk fat and limb fat relative to baseline, 32% had decreases in trunk fat and limb fat, 26% had increased trunk fat and decreased limb fat, and 6% had decreased trunk fat and increased limb fat. Most patients with fat gain had an increase in extremity fat as well, and the changes in peripheral and central fat were significantly and positively correlated.[16] The pattern of regional fat change seen in ACTG 384 is broadly similar to that seen in another prospective study in HIV-positive, treatment-naïve patients initiating antiretroviral treatment, albeit in a smaller patient group ($n = 40$).[17] This study found early gains in both limb and central abdominal fat (evaluated by DXA) during the first 6 months of treatment, followed by a progressive decline in limb fat but maintenance of central abdominal fat.[17] While the initial gains in limb and central abdominal fat, which were accompanied by an increase in lean mass and coincided with the greatest improvements in $CD4^+$ cell count and HIV viremia, likely represent general improvement in health, the maintenance of increased abdominal fat and progressive loss of limb fat over long-term treatment (mean 96 weeks of follow-up) reflect characteristic fat abnormalities seen with HIV treatment.

Risk factors and proposed mechanisms for peripheral lipoatrophy differ from those of central fat accumulation.[18] Lipohypertrophy has been variably linked with use of some

protease inhibitors (PIs) as well as disturbances in adipocyte biology, while peripheral lipoatrophy seems related to the use of thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs) and mitochondrial toxicity.[19–22] However, the effects of antiretroviral therapy on specific fat depots might not be linked to a single drug class.[16,23]

Although the two processes do not necessarily occur in tandem, a mechanism linking peripheral lipoatrophy and fat accumulation has been proposed. Patients who present with both peripheral lipoatrophy and central fat accumulation might have defective postprandial fatty acid disposal and storage by peripheral adipocytes.[24] Based on their research comparing patients with HIV with both conditions and age-matched HIV-negative controls, Sekhar et al.[24] hypothesized that patients with peripheral lipoatrophy/central adiposity have accelerated lipolysis (primarily in the femoral–gluteal region) and release of fatty acids for hepatic reesterification (leading to hypertriglyceridemia), along with decreased clearance of chylomicron triglyceride. A greater proportion of the released free fatty acid was found within the plasma rather than taken into the adipocyte in these patients, suggesting that there was an adipocyte defect resulting in impaired fat storage. While more research is required to more firmly establish this proposal, it could explain a possible link between peripheral lipoatrophy and visceral adiposity in patients with HIV who present with both conditions.

Prevalence

Given the controversy surrounding fat accumulation, the inconsistent patient inclusion criteria for various studies, and the differing methods used to quantify VAT, it is difficult to determine the prevalence of clinically significant central or visceral fat accumulation among the HIV-positive population. A PubMed literature search of studies published to March 2007 involving more than 100 patients and reporting *subjective* outcomes relating to central fat accumulation (increased abdominal girth, abdominal lipohypertrophy, abdominal enlargement, central or abdominal fat accumulation, truncal obesity, central fat gain, increased abdominal wall thickness and/or pseudo-obesity) found prevalence estimates ranging from 13% to 58% (median 30%) of HIV-infected patients (K.A. Lichtenstein, personal communication, 2007). Data based on concordance of patient self-report and physical examination from the FRAM study indicate that approximately 30% of men and 50% of women infected with HIV have abdominal lipohypertrophy, while prevalence rates for lipoatrophy at different sites (cheeks, face, arms, buttocks, legs) range from 11% to 24% in men and from 11% to 16% in women.[4,12]

Anthropometric measurements, such as waist circumference and waist:hip ratio (WHR), and assessment of regional fat content by DXA, cannot distinguish SAT from VAT. Accumulation of VAT can only be differentiated from centralized obesity, and quantified, by CT or MRI scanning, radiographic techniques that provide specific information on the mass and location of visceral and subcutaneous fat. Figure 1 illustrates SAT and VAT on CT scan seen in a healthy individual (Fig. 1A), an obese HIV-negative individual with excess SAT (Fig. 1B) and a patient with HIV-associated visceral fat accumulation (Fig. 1C). MRI and CT are costly and not generally feasible in routine clinical practice. Waist circumference and WHR are convenient measures by which to estimate central fat accumulation, and are important predictors of cardiovascular risk in the general population,[25] although the fact that WHR can be elevated by an increase in waist circumference or a decrease in hip circumference can lead to difficulties in interpretation.[13] Often, an astute clinician can differentiate visceral from subcutaneous fat by physical examination. The presence of both elevated WHR and excess waist circumference is indicative of visceral fat accumulation.

Association with metabolic changes and cardiovascular risk

Observations from the general population show that abdominal obesity, as determined by WHR, is linked with metabolic and cardiovascular complications, including acute myocardial infarction (MI)[25] and insulin resistance.[26,27] Specifically, visceral fat appears to be a more important determinant of insulin resistance than subcutaneous abdominal fat,[28] and in a recent study comparing lean insulin-sensitive to lean insulin-resistant subjects and obese insulin-resistant subjects, differences in visceral fat were found to explain much of the atherogenic lipoprotein profile associated with obesity and insulin resistance.[29]

Consistent with findings in the non-HIV–infected population, abdominal obesity has a significant impact on metabolic parameters and cardiovascular risk in HIV-positive individuals. A study in HIV-positive women found that, among various body composition parameters, WHR was the most significant predictor of C-reactive protein, adiponectin, fasting insulin, 120-minute glucose, and high-density lipoprotein (HDL) cholesterol levels.[30] The increases in cardiovascular risk indices with abdominal obesity appear to translate into increased occurrence of cardiovascular events. Hadigan and colleagues[31] found that the increased 10-year coronary heart disease risk observed in HIV-positive subjects, compared to controls, was partly mediated by increased abdominal obesity, determined by excess WHR. Abdominal obesity is also linked with hyperinsulinemia among HIV-positive men, in whom WHR has been found to be an independent predictor of fasting insulin concentrations.[32]

Hadigan and colleagues[33] compared 71 HIV-infected patients with lipodystrophy, 30 HIV-infected subjects without lipodystrophy, and 213 age- and body mass index (BMI)-matched healthy volunteers. Interpreting the results is challenging as, among those with lipodystrophy, 11 subjects had lipoatrophy, 13 had fat accumulation, and the remaining 47 were described as having combined lipoatrophy and lipohypertrophy. Compared to healthy controls, significantly greater proportions of lipodystrophy patients had elevated measures for fasting insulin, impaired glucose tolerance, total cholesterol and triglycerides (Fig. 2A); these differences were not apparent in HIV-infected patients without lipodystrophy (Fig. 2B). Overall, patients with lipodystrophy had significantly higher WHR than healthy volunteers did, and their significantly greater risks for fasting hyperinsulinemia, impaired glucose tolerance, and hypertriglyceridemia persisted after adjustment for WHR. While there is debate regarding the degree to which VAT might contribute to insulin resistance in the general population,[34] there is evidence to support a causal relationship.[35] Studies in patients without HIV infection have demonstrated that visceral fat accumulation increases free

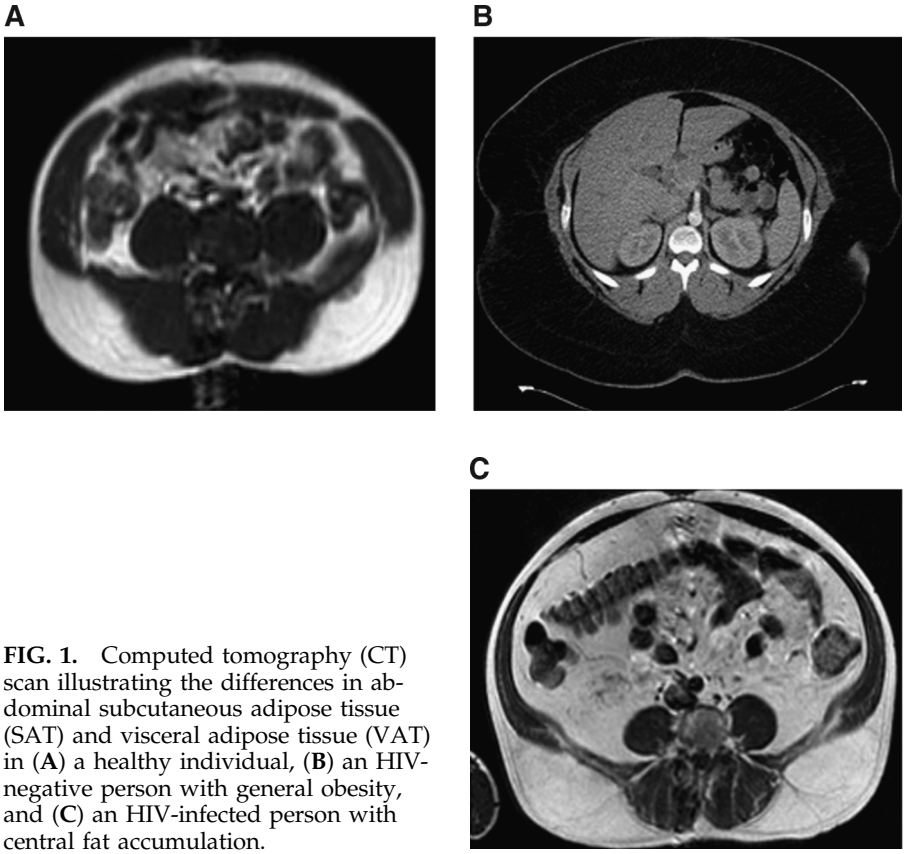

FIG. 1. Computed tomography (CT) scan illustrating the differences in abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in (**A**) a healthy individual, (**B**) an HIV-negative person with general obesity, and (**C**) an HIV-infected person with central fat accumulation.

fatty acid (FFA) release into the portal vein, and long-term exposure to elevated FFA levels causes resistance to the effects of both insulin and glucose on adipose tissue lipolysis and triglyceride storage.[36,37] Significantly elevated fasting and 2-hour post-glucose–load FFA levels have been observed in HIV-infected patients who have signs of altered fat distribution (self-report of increased truncal fat or facial or peripheral lipoatrophy, confirmed by physical examination),[38] and post-glucose–challenge FFA levels were shown to positively correlate with VAT area in a study of nondiabetic HIV-infected patients with abnormal fat distribution (excess WHR and evidence of central fat accumulation or lipoatrophy).[39]

The extent to which these metabolic abnormalities are related to visceral adiposity in HIV-infected patients has not been fully elucidated. Use of combination antiretroviral therapy, particularly use of some PIs, is independently linked with an increased risk of MI in HIV-positive patients.[40,41] In HIV-infected women, carotid artery intimal medial thickness (IMT), a marker of coronary atherosclerosis severity, was increased in PI-treated patients in comparison with non-PI treated patients and healthy controls. In addition, waist circumference, a measure of abdominal obesity, was found to predict IMT in these HIV-infected women,[42] suggesting a possible link between treatment-mediated alterations in central adiposity and cardiovascular outcomes.

Health-related quality of life and antiretroviral treatment adherence

While visceral accumulation has been associated with various metabolic problems such as dyslipidemia, insulin resistance, and increased risk of heart disease, another important consequence of body shape changes is their psychological and sociological impact. Studies of both men and women with HIV-related body shape changes (fat atrophy or hypertrophy), based on patient self-report confirmed by physical examination, showed significantly poorer body image compared with HIV-infected patients without lipodystrophy.[10, 11] Data specifically pertaining to patients with HIV with excess truncal fat show significantly worse general perceived health scores than in age- and gender-matched HIV-negative patients with other chronic conditions known to adversely affect quality of life.[8] Some studies have suggested that patient perception of alterations in body fat distribution is associated with reduced adherence to antiretroviral therapy,[43,44] but others indicate no effect on adherence.[45,46] Given that body shape changes are troublesome to patients, may impact therapy adherence and are associated with a number of metabolic abnormalities that likely increase cardiovascular risk, treatment of fat changes should be considered.

Treatment Options for Central Fat Accumulation in HIV

Non-drug therapy: Lifestyle and dietary interventions

The data evaluating the effects of exercise in HIV-infected patients with central fat accumulation are limited and show mixed results. Most studies are short term, include a limited number of patients and use a variety of inclusion criteria. Two small, 16-week studies conducted in HIV-positive men and women with evidence of central fat accumulation have reported some favorable outcomes in patients undergoing a

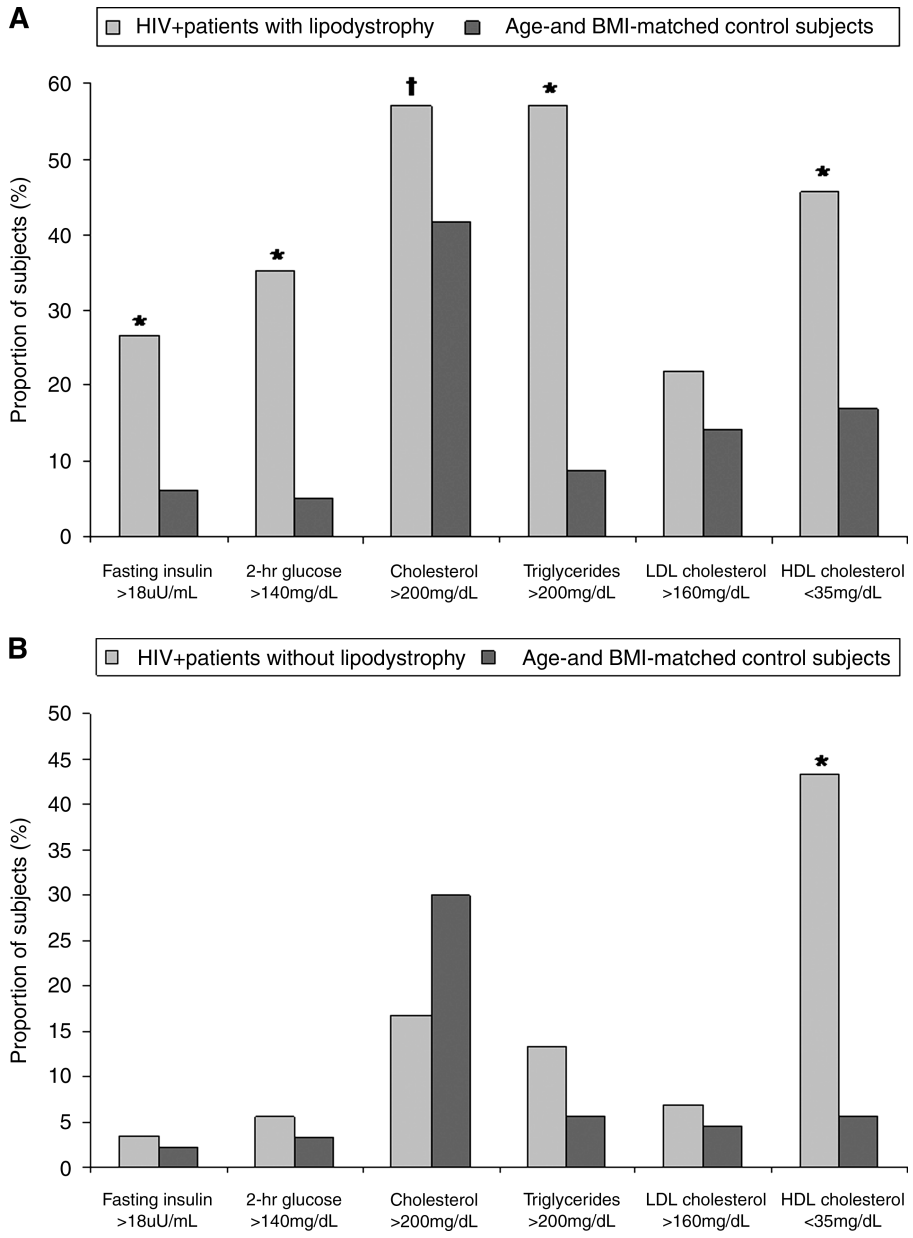

FIG. 2. **A:** Rates of metabolic and lipid abnormalities among 71 HIV-infected patients with lipodystrophy and 213 age- and body mass index (BMI)-matched control subjects. *$p = 0.001$ versus control; †$p = 0.03$ versus control. **B:** Rates of metabolic and lipid abnormalities among 71 HIV-infected patients without lipodystrophy and 213 age- and body mass index (BMI)-matched control subjects.[33] *$p = 0.001$ versus control. Reproduced with permission from Hadigan C, Meigs JB, Corcoran C, et al.[33] Reproduced with permission. © The University of Chicago Press. HDL, high density lipoprotein; LDL, low density lipoprotein.

combined program of aerobic exercise and progressive resistance training.[47,48] The uncontrolled study in men ($n = 10$) showed that 16 weeks of exercise induced a statistically significant 2% decrease in total body fat from baseline (−1.1 kg, $p = 0.03$), mostly occurring within the trunk.[48] The other, which was a randomized comparison of exercise versus no exercise in women with HIV and fat accumulation, showed a modest reduction in waist circumference in the exercise group, but no change in total fat, SAT area, VAT area or lipid levels.[47] In contrast, a 4-month aerobic exercise program in 17 "lipodystrophic" patients (15 with documented fat accumulation and/or lipoatrophy) was associated with preferential loss of VAT (−12%, $p < 0.001$ versus baseline) and significant improvements in total cholesterol, triglyceride, and HDL cholesterol levels.[49] Finally, a study of 37 patients suggested that combining metformin treatment with exercise training for 3 months was more effective than metformin alone in reducing median WHR and fasting insulin levels, with greater reductions in both abdominal SAT and VAT.[50] At completion of the study, VAT area had increased by 1 cm^2 in the metformin monotherapy group and decreased by 17 cm^2 in the metformin plus exercise group ($p = 0.063$); corresponding changes in abdominal SAT were −1 cm^2 and −13 cm^2 ($p = 0.049$). However, the median change in VAT:SAT ratio did not differ between the two treatment groups.

Exercise and dietary interventions have been investigated in HIV-infected patients presenting with hyperlipidemia, general obesity or metabolic syndrome. Adding a 12-week exercise program and a low-lipid diet had no additional effect on body weight, body fat or WHR in a study of 30 HIV-positive patients with lipodystrophy (mean baseline WHR 0.91–0.94) characterized by hyperlipidemia.[51] A 12-week study of a reduced-calorie diet combined with aerobic and resistance exercise in 18 HIV-infected women with general

Table 1. Results from Randomized Controlled Trials Investigating Drug Therapy in the Treatment of Central Fat Accumulation in HIV-Positive Patients

Reference	*Study design*	*No. patients*	*Inclusion criteria*	*Active treatment*	*Quantitative changes in adipose tissue*	*Other outcomes*
Metformin						
Hadigan et al. 2000[71]	r, db, pc 3 months	26	IGT, WHR > 0.9 (men) or > 0.8 (women)	Metformin 500 mg bid	↓VAT ($p = 0.08$) ↓SAT ($p = 0.08$) No significant change in VAT:SAT ratio	↓WC ($p = 0.02$) ↓DBP ($p = 0.009$)
			Fat accumulation in trunk, breast, or neck, and/or fat loss in face or extremities, on physical examination			No significant changes in lipids
Kohli et al. 2006[72]	r, db, pc 24 weeks	48	WHR ≥ 0.95 (men) or ≥ 0.85 (women) Self-reported increase in abdominal girth	Metformin 1500 mg/d	No significant change in VAT	↓ appendicular fat No significant changes in lipids
Mulligan et al. 2006[73]	r, db, pc 16 weeks	105	Hyperinsulinemia WHR > 0.95 (men) or > 0.85 (women)	Metformin 500–1000 mg bid, rosiglitazone 4 mg od, or combination	No significant change in VAT	↑ lower extremity fat with rosiglitazone monotherapy
Driscoll et al. 2004[50]	r 3 months	37	Hyperinsulinemia WHR > 0.90 (men) or > 0.85 (women) Lipodystrophy score > 2	Metformin 500–850 mg bid ± aerobic and resistance exercise training	↓ VAT ($p = 0.063$ with metformin + exercise vs. metformin alone) No significant change in VAT:SAT ratio	
Recombinant human growth hormone (rhGH)						
Kotler et al. 2004,[88] 2006[89]	r, db, pc 24 weeks (12-weeks induction and 12-week maintenance)	245	Normal glucose metabolism Normal triglyceride levels WHR > 0.95 and WC > 88.2 cm (men) or WHR > 0.90 and WC > 75.3 cm (women)	Induction: rhGH 4 mg AD or DD Maintenance: rhGH 4 mg AD	*rhGH 4mg DD induction and 4mg DD maintenance*: ↓ VAT at week 12 (−18.8%, $p < 0.001$) ↓ VAT at week 24 (−21.4%; $p \leq 0.001$ vs baseline) *rhGH 4mg AD induction and 4mg AD maintenance* ↓ VAT at week 12 (−16.8%, $p < 0.001$) ↓VAT at week 24 (−10.7%, $p \leq 0.001$) vs baseline)	↓ non-HDL cholesterol
Grunfeld et al. 2007[7]	r, db, pc 36 weeks (12-week induction and 24-week maintenance)	325	Normal glucose metabolism WHR ≥ 0.95 and WC > 88.2cm (men) or WHR ≥ 0.90 and WC > 75.3 cm (women)	*Induction:* rhGH 4 mg DD *Maintenance*: rhGH 2 mg AD	*Induction*: ↓VAT at week 12 (−20.3%, $p < 0.001$)	↓ non-HDL cholesterol

					Maintenance: <50% of patients responding to rhGH induction went on to gain >50% of their lost VAT	↑ HDL cholesterol ↑ HDL:LDL cholesterol ratio Significant improvements in HRQOL measures for depression and general perceived health (87)
Lo et al. 2008[91]	r, db, pc 18 months	56	Lipodystrophy and peak GH < 7.5 ng/mL by GHRH-arginine stimulation	rhGH average 4.1 μg/kg/d	↓ VAT at month 18 (−22 vs. −4 cm^2, $p = 0.049$) ↓ trunk-to-extremity fat ratio (−0.4 vs. −0.007; $p = 0.0002$) ↓ trunk fat (−0.5 vs. + 0.2 kg; $p = 0.04$)	↓ DBP and ↓ triglycerides No significant change in carotid IMT
Growth hormone releasing hormone (GHRH)						
Koutkia et al. 2004[93]	r, db, pc 12 weeks	31 men	WHR ≥ 0.90 Increased abdominal girth or fat loss in face or extremities	GHRH 1mg bid	↓ VAT (−19.2%, $p = 0.07$) ↓ VAT:SAT ratio (−0.19, $p = 0.02$)	No significant changes in lipids
Falutz et al. 2005[94]	r, db, pc 12 weeks	61	WHR ≥ 0.94 and WC ≥ 95cm (men) or WHR ≥ 0.88 and WC ≥ 94 cm (women)	GHRH 1 or 2 mg od	No significant change in VAT ↓ VAT:SAT ratio (−0.14 with 2 mg dose, $p = 0.008$)	↓ non-HDL cholesterol ↓ Triglycerides ↓ Cholesterol:HDL ratio
Falutz et al. 2007[95]	r, db, pc 26 weeks	412[a]	WHR ≥ 0.94 and WC ≥ 95 cm (men) or WHR ≥ 0.88 and WC ≥ 94 cm (women)	GHRH 2 mg od/d	↓ VAT (−15.2%, $p < 0.001$) ↓ VAT:SAT ratio (−15.5%, $p < 0.001$)	↓ Triglycerides ↓ Cholesterol:HDL ratio

[a]Nineteen percent of patients had type 2 diabetes at baseline.

All p values relate to comparisons with placebo unless otherwise stated.

AD, alternate days; bd, twice daily; db, double-blinded; DBP, diastolic blood pressure; DD, every day; GHRH, growth hormone releasing hormone; HDL, high-density lipoprotein; HRQOL, health-related quality of life; IGT, impaired glucose tolerance; IMT, intima-media thickness; ns, not significant; od, once daily; pc, placebo comparison; r, randomized; rhGH, recombinant human growth hormone; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist:hip ratio.

obesity (BMI $\geq 30\,kg/m^2$) led to significant reductions in waist circumference (-6.1 cm, $p = 0.0003$) but not WHR. The volumes of both VAT (-17%, $p < 0.0001$) and SAT (-15%, $p < 0.0001$) declined significantly; there was no change in the overall VAT:SAT ratio and no improvements in glucose or lipid metabolism.[52] Finally, a randomized study investigated an intensive lifestyle intervention comprising weekly 1-to-1 counseling sessions focusing on healthy eating and, to a lesser extent, weight loss, in HIV-positive subjects with metabolic syndrome.[53] At 6 months, patients assigned to the program experienced a mean 2.6 cm decrease in waist circumference ($p < 0.05$ versus baseline and control group), but there were no significant improvements in lipid levels, fasting glucose or insulin resistance. Although there are currently no dietary recommendations for HIV patients with central fat accumulation, there may be a rationale for reducing dietary fat, while maintaining moderate amounts of protein, and adding fiber. A case-control study from the Nutrition for Healthy Living cohort has shown that HIV patients without fat deposition had diets higher in total protein, dietary fiber, and pectin, and undertook greater amounts of resistance training, compared with those who had developed fat deposition (WHR > 0.95).[54] In another study in HIV lipodystrophic patients (with fat redistribution characterized as loss of subcutaneous fat from the face and extremities and/or accumulation of fat around the neck, dorsocervical region, abdomen or trunk; mean waist circumference was 91 cm in men and 108 cm in women), dietary intake of total protein and animal protein was positively correlated to total cholesterol, triglyceride, and non-HDL cholesterol levels, and intake of trans fat was positively correlated with triglyceride level.[55] Negative correlations were found between soluble fiber intake and levels of total cholesterol or triglycerides. The hypertriglyceridemia often seen in patients with HIV and VAT accumulation might be a direct result of impaired ability to metabolize dietary fat.[24] The optimal dietary regimen for lipodystrophy patients with central fat accumulation and the role of exercise is an important area for further study.

Switching antiretroviral therapy

One approach to treating visceral fat accumulation has been to change antiretroviral therapy. Although there might be some modest reversals of peripheral lipoatrophy by eliminating thymidine analogues,[56–58] it has not been shown to reduce VAT. A number of studies have explored switching off a PI-based regimen (see reviews by Hansen et al.[59] and Drechsler and Powderly[60]). Improvements in the lipid profile and glucose metabolism have been described, but this approach does not appear to reduce abdominal fat accumulation. These studies have used a wide variety of definitions and methods of assessment, making difficult a definitive statement on the effect on fat distribution of switching from a PI. Newer PIs such as atazanavir appear to have a more favorable metabolic profile,[61] and preliminary data suggest switching to atazanavir can ameliorate hyperlipidemia in antiretroviral-experienced patients.[62] However, data on the impact of such switches on body fat distribution are lacking.

Surgery

There have been reports of successful surgical treatment for some areas of lipohypertrophy in patients with HIV using various techniques including suction- or ultrasonography-assisted liposuction,[63,64] mammoplasty,[65] or direct excision.[63] Patients report improved appearance as well as increased range of motion, decreased neck strain and improved posture after dorsocervical liposuction.[63] Liposuction has also been used to remove fat from the anterior neck, abdomen, and flanks in patients with HIV,[63,64] but liposuction does not remove deep visceral fat, and the procedure may be more difficult in HIV-positive patients because of the tenacity of the fat tissue.[64] Estimates suggest approximately 25% of patients will develop a recurrence of lipohypertrophy after liposuction.[63] Surgery is not an option for patients with uncontrolled disease, and preoperative screening should include T cell count, nutritional status, viral load and compliance with antiretroviral medications.[65] Patients and physicians should also be aware that the surgical wounds of people with HIV have a lower tensile strength than wounds from an HIV-negative individual.[65]

Antidiabetic medications

It has been postulated that medications used to treat type 2 diabetes might be useful in reversing insulin resistance and improve abnormalities in fat associated with HIV treatment.

The use of thiazolidinediones, such as rosiglitazone or pioglitazone, which are currently approved for treating type 2 diabetes, has been evaluated in HIV-positive patients with lipodystrophy predominantly characterized by lipoatrophy. Some of these studies have shown some improvement in peripheral fat loss,[66,67] although no effect was seen in others.[68,69] However, none of these studies has shown a beneficial effect on VAT as assessed by abdominal CT or MRI.[66–69] This lack of effect on VAT is consistent with previous studies of thiazolidinediones in non-HIV–infected diabetic patients.[70]

Studies of metformin on visceral fat accumulation in HIV-infected patients have shown mixed results (Table 1).[71–73] In a small, randomized, placebo-controlled study enrolling 26 patients with impaired glucose tolerance and/or hyperinsulinemia, excess WHR and evidence of truncal fat accumulation and/or peripheral lipoatrophy, metformin 500 mg given twice daily significantly reduced insulin levels on oral glucose challenge,[71] and was associated with significant reductions in weight, waist circumference, and a trend toward reduced VAT. The proportionate decrease in SAT meant that the overall VAT:SAT ratio was unchanged relative to placebo treatment and there was no significant effect on the WHR. In another small, randomized, placebo-controlled study enrolling HIV-positive patients with self-reported increases in abdominal girth and with excess WHR and normal glucose tolerance, 24 weeks of treatment with metformin 1500 mg/d had no effect on VAT or lipid parameters, but did have the troublesome effect of significantly reducing limb fat.[72] Taken together, these findings suggest that, in treating visceral fat accumulation, metformin should be reserved for patients with impaired glucose tolerance or diabetes and no evidence of lipoatrophy. A recent study of combining metformin with rosiglitazone, compared with either monotherapy, in the treatment of HIV-positive patients with hyperinsulinemia and elevated WHR[73] found no significant differences between treatment groups regarding changes in abdominal VAT, although there was a high rate of treatment discontinuation in the metformin monotherapy group, which hampers interpretation of the study results.

Hormonal treatment

Testosterone replacement or anabolic steroids. Although testosterone replacement and/or anabolic steroid therapy has proven useful in treating HIV-associated hypogonadism,[74] androgen therapy has not been found useful for treating abdominal obesity or VAT accumulation. A randomized, placebo-controlled 24-week trial of 10 g testosterone gel (twice the standard replacement dose) or placebo given to 88 HIV-positive men with excess WHR (>0.95) or waist circumference (>100 cm) showed no effect on VAT. At entry, these HIV-infected men were on stable antiretroviral therapy and had low or low-normal testosterone levels (defined as total testosterone levels of 125–400 ng/dL, or bioavailable testosterone less than 115 ng/dL, or free testosterone less than 50 pg/mL).[75] Testosterone treatment was associated with decreased total and subcutaneous abdominal fat and increased lean mass, compared to placebo, but there was no significant difference between the testosterone and placebo groups in median change from baseline in VAT. Testosterone-treated men showed a decrease in extremity fat, compared with the placebo group, which suggests testosterone supplementation should be used with caution in patients with underlying lipoatrophy.

There are limited data on the effect of anabolic steroids on fat accumulation. A cross-sectional study investigated the incidence of body habitus changes (facial atrophy, visceral fat increases, and peripheral fat decreases on visual assessment) in 725 HIV-positive patients, 190 of whom were taking nandrolone or oxandrolone.[76] They found that 12.3% of nandrolone recipients and 4% of oxandrolone recipients had body habitus changes, rates lower than may be expected in a population taking PIs. However, the effect of synthetic anabolic steroids on VAT accumulation has not been investigated prospectively.

Growth hormone therapy. Growth hormone (GH) deficiency, irrespective of the cause, is associated with visceral adiposity,[77] and obese individuals are known to have lower than normal levels of GH secretion and a blunted response to GH secretagogues.[78,79] Consistent with these findings, a study by Rietschel and colleagues demonstrated that HIV-positive men with central fat accumulation had significantly reduced GH secretion compared with both HIV-negative controls and HIV-infected controls without fat accumulation, all age- and BMI-matched, suggesting that GH deficiency was not a result of HIV infection *per se*.[80] There was an inverse relationship between GH secretion and VAT in the HIV-positive men (Fig. 3). While VAT area predicted mean GH level in HIV-positive patients in this study, only BMI predicted mean GH levels in HIV-negative patients. Evidence from studies in non-HIV–infected subjects supports the effectiveness of GH therapy for the reduction of VAT in abdominally obese individuals[81] and in GH-deficient individuals.[77,82] Also in GH-deficient patients, GH treatment improves inflammatory markers that are predictive of cardiovascular events.[83]

Early studies of GH therapy in HIV lipodystrophy patients reported some improvements in truncal adiposity and VAT,[84–87] and these results have been confirmed in two large-scale trials (Table 1).[7,88,89]

Kotler et al.[88] conducted a randomized, placebo-controlled study comparing 3 recombinant human growth hormone (rhGH) regimens in 245 patients with normal glucose metabolism, normal triglyceride levels and anthropometric measurements indicative of excess VAT (WHR > 0.95 and waist circumference > 88.2 cm in men or WHR > 0.90 and waist circumference > 75.3 cm in women). During the initial 12 weeks of treatment, rhGH significantly reduced VAT area (assessed by CT) by 18.8% ($p < 0.001$) when administered at a dose of 4 mg/d and by 16.8% ($p < 0.001$) when administered at a dose of 4 mg every alternate day. After a second 12 weeks maintenance on rhGH 4 mg every alternate day, the decrease from baseline in VAT area was 10.7% and 21.4% ($p \leq 0.001$), respectively, for those who began with 4 mg/d or 4 mg every alternate day.[89] Abdominal SAT also decreased significantly with 12 weeks of treatment with rhGH 4 mg daily ($p < 0.001$) or 4 mg on alternate days ($p = 0.044$); however, at week 24, the change from baseline in SAT was significant only in the group that received daily dosing initially and then continued to receive rhGH maintenance treatment (overall reduction of 18.5 cm^2; $p = 0.0019$).[89] Modest reductions in non-HDL cholesterol of −5.2% and −4.5% (respectively for 4 mg daily and 4 mg every alternate day followed by 4 mg alternate day maintenance) were apparent at completion of the 24-week regimen ($p < 0.05$ versus baseline).[88]

Another randomized, placebo-controlled trial of 325 subjects had similar inclusion criteria and incorporated a 12-week induction phase (comparing rhGH 4 mg/d versus placebo) and a 24-week maintenance phase (comparing rhGH 2 mg on alternate days versus placebo).[7] During the induction phase, patients treated with rhGH 4 mg/d had a significantly greater reduction in VAT than placebo recipients (−20.3% versus + 3.6, $p < 0.001$), as well as significantly greater reductions in trunk fat (−20% versus + 1.4%, $p < 0.001$), abdominal SAT (−7.1% versus + 1.6%, $p < 0.001$) and limb fat (−6.0% versus + 2.8%; $p < 0.001$) and improvements in the lipid profile. During maintenance therapy, 60% of the 75 patients who responded to active induction therapy with rhGH 4 mg/d subsequently kept off more than half of the VAT lost during weeks 12–36, meeting the predefined efficacy criterion. The mean percentage change in VAT area from baseline to week 36 was statistically significant in the rhGH maintenance arm (−3.5%, $p = 0.018$) but not the placebo maintenance arm (+3.1%, $p = 0.103$) though the between-group difference did not reach statistical significance. Initial significant reductions in abdominal SAT ($p < 0.001$) and limb fat ($p < 0.001$) during induction were not maintained during maintenance treatment and the overall change in these parameters between baseline and week 36 in the rhGH group was not statistically significant.[7] Importantly, reductions in VAT and trunk fat during induction treatment were accompanied by significant patient-reported improvements in body image.[90]

Adverse events occurring with rhGH treatment in these two trials were generally mild or moderate in severity and included those expected with GH treatment, such as arthralgia, myalgia and peripheral edema.[7,88] Transient increases in fasting serum insulin and insulin area under the curve (AUC) occurred during rhGH induction treatment, but levels returned to baseline after treatment discontinuation.[7,88] Fasting glucose and glucose levels 120-minute post-oral glucose tolerance test also increased, but remained within normal bounds at completion of maintenance treatment, and there were no clinically significant increases in glycosylated hemoglobin in either trial, both of which enrolled only normoglycemic patients.

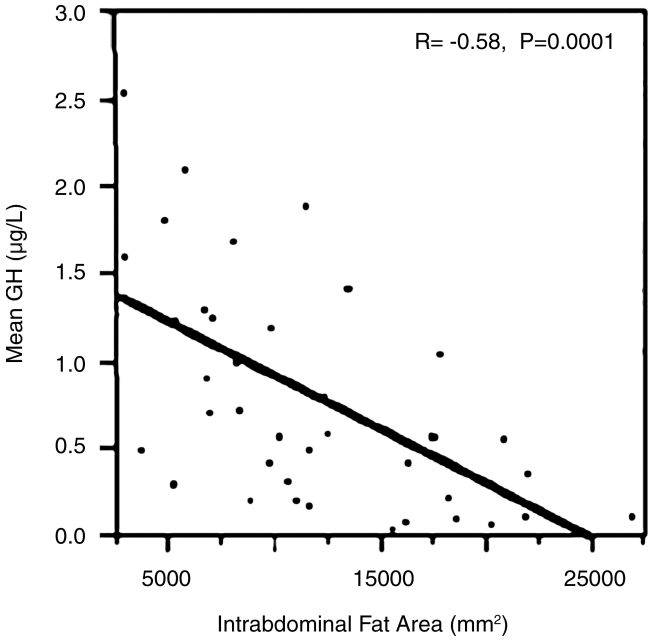

FIG. 3. Relationship between visceral fat and mean overnight growth hormone (GH) concentration in HIV-infected men. Reproduced with permission from Rietschel P, Hadigan C, Corcoran C, et al.[80] © 2001 The Endocrine Society.

There are currently limited data on the long-term use of rhGH treatment for patients with central fat accumulation. However, a recent study examined the effect of 18 months' treatment with low-dose rhGH treatment (average 4.1 μg/kg per day) in 56 patients with HIV-associated lipodystrophy and relative GH deficiency (peak GH $<$ 7.5 ng/mL after stimulation).[91] After 18 months, patients randomized to rhGH had significant reductions in VAT area ($p = 0.049$), trunk-to-extremity fat ratio ($p = 0.0002$) and trunk fat area ($p = 0.04$) compared with placebo recipients. Diastolic blood pressure and triglyceride levels were also significantly lower in the active treatment group than the placebo group. However, there was no change in the carotid IMT, and patients on rhGH had an increase in insulin-like growth factor (IGF)-1 levels and blood glucose levels 2 hours after an oral glucose challenge.[91] A recent study conducted in 64 patients with lipodystrophy, 35 of whom had signs of visceral adiposity (excess waist circumference and increased WHR), suggests that the addition of rosiglitazone may abrogate a rise in insulin resistance that accompanies GH therapy.[92] More research is needed into the optimal approach to maintaining the benefits of rhGH therapy over the long term, since most patients tend to regain VAT once treatment is stopped.[7]

GH-releasing factor. In an attempt to circumvent potential adverse side effects from exogenous GH administration, growth hormone releasing hormone (GHRH) is being investigated for the treatment of HIV-associated fat accumulation (Table 1). It is hoped that this approach will elicit GH secretion in a pulsatile pattern that more closely mimics normal physiology. The feasibility of this approach was demonstrated by Koutkia et al.,[93] who examined changes in IGF-I levels in response to GHRH treatment in 31 men who had an elevated WHR in the presence of increased abdominal girth or peripheral or facial fat loss. IGF-I concentrations provide an integrated measure of GH secretion, which is pulsatile in nature. Treatment for 12 weeks with GHRH 1 mg twice daily effectively increased IGF-I concentrations and was also associated with improvements in total and regional body composition including significantly reduced truncal fat, a trend toward reduced VAT area and a significant reduction in the abdominal VAT:SAT ratio. These results were partially confirmed by another 12-week study in 61 HIV-infected patients with high WHR and waist circumference, in which GHRH analogue 2 mg/d significantly reduced truncal fat.[94] There was a decrease in VAT and an increase in SAT that did not reach statistical significance relative to placebo, but overall there was a significant improvement in the VAT:SAT ratio. Results from a larger trial enrolling 412 HIV-infected patients with excess WHR and excess waist circumference, 19% of whom had type 2 diabetes or glucose intolerance at baseline, demonstrated a significant reduction in VAT area after 26 weeks of GHRH analog treatment (-15% versus $+5\%$ with placebo, $p < 0.001$), with little effect on SAT and no effect on limb fat.[95] Significant reductions in triglycerides and the total cholesterol:HDL cholesterol ratio were also observed with GHRH analogue compared to placebo ($p < 0.001$). Adverse events were generally similar in the two treatment arms, although the rate of drug-related adverse events was significantly higher in the GHRH group (53.8% versus 36.5%; $p < 0.001$), and 2.2% of GHRH analogue-treated patients (and no placebo recipients) experienced urticaria beyond the injection site, which led to study withdrawal. Importantly, no significant changes from baseline were noted in fasting or 2-hour glucose and insulin at completion of the study.

Conclusions

Changes in body shape and fat composition cause distress to many patients living with HIV infection and are associated with worrisome metabolic changes that likely portend cardiovascular risk. For patients newly diagnosed with HIV infection, there is the hope that proper selection of antiretroviral agents, coupled with close monitoring and early action, will minimize pathologic fat alterations and metabolic problems. However, at least one third of HIV-positive patients receiving antiretroviral therapy already have such body dysmorphic problems and there is currently very little to offer patients with VAT accumulation.

There are data to support the role of changing a patient's HAART regimen to improve some metabolic parameters as well as lipoatrophy, but data on their effect on fat accumulation are generally lacking. Changing HAART is often not a realistic option in clinical practice. The data on non-drug interventions such as diet and exercise have come from small studies, and results are modest at best. More research needs to be done in this area. A number of therapeutic agents, primarily used to treat diabetes mellitus, have been evaluated in clinical studies, often with disappointing or even adverse results. Currently, no pharmacologic therapies have an approved indication for treatment of central fat accumulation, including VAT.

There are data to support the use of both rhGH and GHRH, which require daily injections, in decreasing VAT and improving metabolic parameters. For patients with visceral fat

accumulation, these compounds show promise in reducing VAT and improving metabolic parameters, as well as decreasing emotional distress over body shape changes and improving overall quality of life. However, these agents are expensive and much more needs to be known, particularly about their effects during long-term use.[96]

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