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MAJOR ARTICLE

Practical Review of Recognition and Management of Obesity and Lipohypertrophy in Human Immunodeficiency Virus Infection

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Background. Obesity and lipohypertrophy are common in treated human immunodeficiency virus (HIV) infection and contribute to morbidity and mortality among HIV-infected adults on antiretroviral therapy (ART).

Methods. We present a consensus opinion on the diagnosis, clinical consequences, and treatment of excess adiposity in adults with treated HIV infection.

Results. Obesity and lipohypertrophy commonly occur among HIV-infected adults on ART and may have overlapping pathophysiologies and/or synergistic metabolic consequences. Traditional, HIV-specific, and ART-specific risk factors all contribute. The metabolic and inflammatory consequences of excess adiposity are critical drivers of non-AIDS events in this population. Although promising treatment strategies exist, further research is needed to better understand the pathophysiology and optimal treatment of obesity and lipohypertrophy in the modern ART era.

Conclusions. Both generalized obesity and lipohypertrophy are prevalent among HIV-infected persons on ART. Aggressive diagnosis and management are key to the prevention and treatment of end-organ disease in this population and critical to the present and future health of HIV-infected persons.

Keywords. human immunodeficiency virus (HIV); obesity; lipohypertrophy; antiretroviral therapy.

Non-AIDS events are leading causes of morbidity and mortality among human immunodeficiency virus (HIV)–infected adults in the modern treatment area. Critical drivers of non-AIDS events are the metabolic and inflammatory consequences of excess adiposity. The prevalence of obesity [1–4] before and after antiretroviral therapy (ART) initiation is increasing worldwide, and central lipohypertrophy persists [5–7]. Aggressive diagnosis and early intervention may prevent end-organ disease in this population. Here, we present a consensus opinion on the diagnosis, clinical consequences, and treatment of excess adiposity in adults with treated HIV infection.

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DEFINITIONS

Overweight and obese states may result from a variety of factors [8], including an imbalance between calories consumed and expended that leads to fat accumulation, and may impair health. Body mass index (BMI) is a simple measure to classify body size in adults. Body mass index is defined as a person's weight in kilograms divided by the square of their height in meters (kg/m^2). The World Health Organization defines obesity as a BMI ≥30 kg/m^2 [9]. Although BMI typically correlates with total percentage of body fat, in persons with low muscle mass, a normal (18.5–24.9 kg/m^2) BMI may represent excess adiposity. For this reason, some authorities define obesity as body fat >25% for men or >33% for women [10]; however, this requires specialized techniques for body fat measurement (such as dual-energy x-ray absorptiometry [DXA] or bioelectrical impedance analysis) that are less standardized and less readily obtainable in clinical practice.

In the setting of treated HIV, lipohypertrophy refers to localized abnormal fat accumulation, most commonly of the intra-abdominal compartment (visceral adipose tissue [VAT]), breasts, dorso-cervical area (buffalo hump), and/or as discrete

accumulations under the skin (lipomas). Lipohypertrophy can occur in >1 regions simultaneously, with or without concurrent peripheral fat loss in the limbs or face (lipoatrophy) [11]. The coexistence of lipohypertrophy and lipoatrophy is referred to as mixed lipodystrophy. The causes of lipohypertrophy are not fully understood. Confounding the matter, generalized obesity and central lipohypertrophy can overlap in an aging population with traditional and HIV-/ART-specific risk factors.

PATHOPHYSIOLOGY

Obesity

Obesity is often multifactorial [8]; sedentary lifestyle and intake of excess or poorer quality calories (saturated fats, processed sugars) are significant risk factors [12]. Age, genetics, comorbid diseases, alcohol, certain medications, and resting metabolic rate also contribute [13]. Additionally, aging is associated with physiologic central fat redistribution, adipocyte senescence, and chronic inflammation [14], which may be enhanced in HIV-infected individuals.

The gut microbiome may play an important role in obesity development [15]. Microbiome alterations in obesity include increased energy harvest from food [16]; altered secretion of gut hormones that affect satiety, such as glucagon-like peptide-1 (GLP-1) [17]; increased lipopolysaccharide shedding [18], leading to activation of inflammatory pathways that promote ectopic fat deposition; production of byproducts that alter insulin–glucose homeostasis [19]; and modulation of innate immunity and the autonomic nervous system [20]. Indeed, increased sympathetic (leading to leptin excess) and parasympathetic (stimulating adipogenesis) nervous system activity have been associated with obesity, particularly central adiposity [21]. Finally, activation of the renin-angiotensin system is associated with visceral adiposity and insulin resistance [22].

Fat type and distribution also influence clinical impact: In HIV-uninfected persons, VAT and subcutaneous adipose tissue (SAT) metabolism and inflammatory signatures vary, with VAT (and particularly hepatic fat) accumulation associated with more pronounced sequelae [23–25]. In HIV-infected persons on suppressive ART, VAT and SAT metabolic and inflammatory signatures are less well understood; however, less proinflammatory signal induction in VAT may protect this depot from fat loss and promote metabolic dysfunction and systemic inflammation [26].

Lipohypertrophy

The etiology of lipohypertrophy in treated HIV infection is multifactorial. There is likely a direct role for HIV: adipose tissue may serve as a reservoir for HIV, altering the local tissue environment and promoting enhanced adipose tissue inflammation [27]. Indeed, altered adipocyte differentiation and enhanced fat inflammation have been reported in ART-untreated HIV controllers [28]. HIV proteins (Tat, Nef, Vpr) alter adipose tissue function and increase inflammation in preclinical models [29]. Finally, the endoribonuclease DICER, which is downregulated by Vpr, is associated with lipohypertrophy and altered brown adipocyte function [30].

HIV-associated chronic inflammation and immune activation may play a direct role in the development of lipohypertrophy, with circulating $CD8^+$ T-lymphocyte activation linked to VAT accumulation [31]. Similar to obesity, hormonal imbalances (eg, hypogonadism, growth hormone deficiency, renin-angiotensin system activation) and gut microbiome alterations may play adjunct roles [32–34].

Antiretroviral therapy's role in lipohypertrophy and VAT accumulation is evolving. Although lipoatrophy in HIV-infected persons is mainly linked to the use of thymidine analog nucleoside reverse-transcriptase inhibitors (NRTIs) [35, 36], in the modern ART era patients are more likely to experience fat increases [37–39], and the role of ART in fat gain remains uncertain [40, 41]. In vitro, ritonavir-boosted protease inhibitors (PIs) induce cellular senescence, oxidative stress and inflammation, and accumulation of the senescence protein prelamin-A in adipose tissue [42], as observed in buffalo hump fat with a brown fat-like phenotype [43, 44]. Additionally, multiple ART classes (including PIs, NRTIs, and non-NRTIs [NNRTIs]) have been associated with impaired adipogenesis, adipocyte differentiation, or function [45, 46]. Impairment of lipid and/or glucose metabolism by these agents further stimulates a proinflammatory environment detrimental to adipose tissue.

Clinical trials have assessed the role of ART in the development of lipohypertrophy. Overall, no differential effect of the NRTI or NNRTI classes has been observed. The integrase strand transfer inhibitor (INSTI) raltegravir led to similar VAT accumulation when compared with PIs [38], but the effects of other INSTIs remain uncertain. The role of PIs also remains uncertain. Although PIs do not generally lead to more lipohypertrophy than NNRTIs [47], ritonavir-boosted atazanavir may be an exception: when this specific PI was compared with NNRTIs and older PIs, there was a trend toward greater gains in central fat [48, 49]. However, ritonavir-boosted atazanavir and darunavir performed similarly in 2 other studies [38, 50].

CONSEQUENCES OF OBESITY AND LIPOHYPERTROPHY

Obesity likely has similar metabolic and inflammatory consequences in HIV-infected persons as in the general population (Figure 1). Obesity and lipohypertrophy, particularly VAT accumulation, are often associated with chronic inflammation in adipose tissue, insulin resistance [51–54], increased metabolic syndrome risk [55], dyslipidemia [56] and increased oxidative stress [57]; abdominal obesity is robustly associated with cardiovascular disease (CVD) risk and mortality [58–60]. However, for any given BMI, HIV infection appears to confer greater

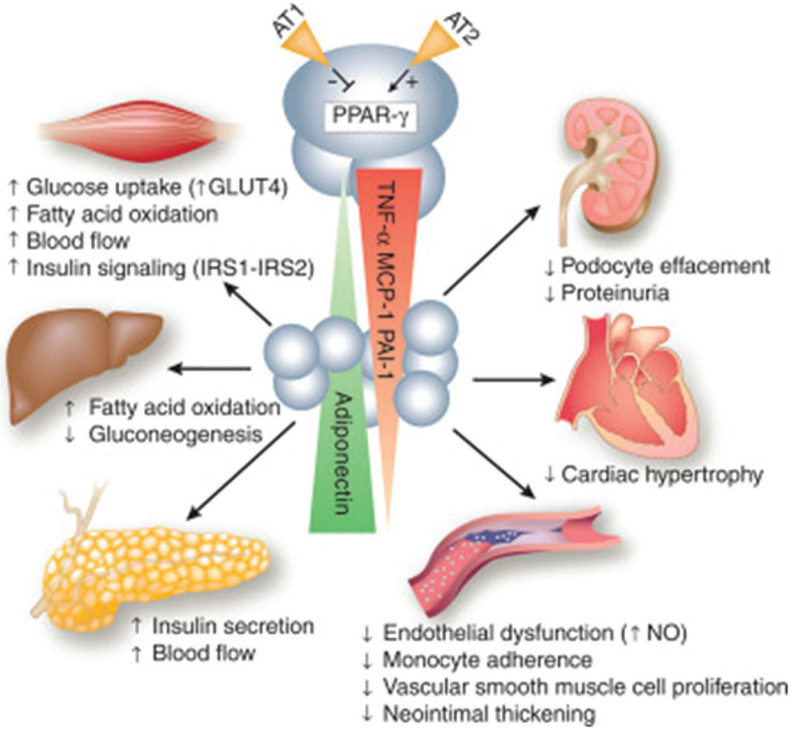

Figure 1. Central role of the adipocyte in multisystem disease. Abbreviations: AT1/AT2, angiotensin II receptor type I/II; GLUT4, glucose transporter type 4; IRS1/2, insulin receptor substrate 1/2; MCP-1, monocyte chemoattractant protein 1; NO, nitric oxide; PAI-1, plasminogen activator inhibitor 1; PPAR-γ, peroxisome proliferator-activated receptor-γ; TNF-α, tumor necrosis factor α. Adapted with permission from Macmillan Publishers Ltd, *Kidney Int* 2008;74(7):851–3.

cardiovascular and metabolic consequences compared with matched HIV-uninfected populations [S61, S62].

Similarly, VAT changes of as little as 5% affect metabolic syndrome risk [S63], and obesity and increased VAT are known risk factors for diabetes mellitus (DM) and CVD [S63]. Obesity and lipohypertrophy are usually pro-inflammatory states, and HIV-associated inflammation and immune activation could facilitate or perpetuate concomitant metabolic disease. Indeed, in some populations, HIV infection is associated with increased type 2 DM [S64] and CVD risk [S65, S66]. Central fat accumulation and ectopic fat deposition may contribute to CVD development through the release of proinflammatory mediators and their downstream effects. In HIV-infected patients, VAT, intrahepatic fat, and epicardial fat are associated with CVD independent of traditional CVD risk factors [S67–S69].

Poorer neurocognitive function was associated with increased waist circumference (WC) among HIV-infected participants in the CHARTER study [25]. Similarly, in the Multicenter AIDS Cohort Study, VAT was strongly associated with regional brain atrophy (which precedes neurocognitive decline), irrespective of HIV serostatus [S70].

Multimorbidity is the accumulation of multiple, serious chronic health conditions. In some cases, these conditions may interact to amplify morbidity and mortality [S71]. For example, obesity is directly associated with detrimental effects on muscle [S72]; obesity is also associated with osteoarthritis, neurocognitive dysfunction, CVD, and DM, which are associated with increased risk of physical function impairment or frailty [S73]. Overweight or obese HIV-infected individuals have a ≥67% prevalence of multimorbidity [S74].

Finally, in addition to metabolic and inflammatory consequences, body fat changes are stigmatizing and may impact self-esteem, affect ART adherence, lead to depression, and decrease quality of life [S75].

CLINICAL ASSESSMENT OF OBESITY, LIPOHYPERTROPHY, AND THEIR SEQUELAE

Body weight and BMI should be tracked at least yearly and weight gain addressed because prevention and early intervention are likely more effective than reversing fat accumulation. Because lower muscle mass [S76] can lower calculated BMI despite an increase in body fat [S77], we recommend annual measurement of WC for all HIV-infected persons [S78, S79]. Elevated WC is indicative of increased cardiometabolic risk regardless of BMI [S80]. Waist circumference cutoffs indicative of increased metabolic risk have been proposed by multiple groups, including the International Diabetes Foundation (≥94 cm for men, ≥80 cm for women) and US National Cholesterol Education Program (>102 cm for men, >88 cm for women) [S80, S81]. A minimum WC of 94 cm in women and 95 cm in men correlates with VAT

area ≥130 cm^2, a validated threshold for increased markers of cardiometabolic risk [S82, S83]. However, the WC cutoffs for metabolic risk and elevated VAT have not been validated in HIV-infected populations.

Although etiology and treatment strategies for generalized obesity and lipohypertrophy may differ, clinical distinction can be difficult because these conditions often coexist. A personal or family history of obesity and diffuse fat distribution supports the diagnosis of generalized obesity, whereas regional truncal or visceral fat accumulation supports the diagnosis of lipohypertrophy. Additionally, lipohypertrophy often becomes clinically visible at least 1–2 years after ART initiation. Although most standardized lipohypertrophy definitions include radiographic assessment of fat quantity [S84], use of imaging is primarily limited to research and not recommended in routine clinical practice [S85–S87]. Furthermore, lipohypertrophy definitions were established in cohorts with a high prevalence of mixed lipodystrophy and extensive exposure to older NRTIs [S88], making the validity of these definitions in the current ART era unknown.

Assessment for complications of obesity and lipohypertrophy should follow established obesity management guidelines [S78], with some notable exceptions: Fasting lipids and glucose should be measured annually and within 3 months of ART change [S89]. Dyslipidemia should be managed per available consensus guidelines [S90, S91], with the caveat that existing CVD risk scores may underestimate risk in HIV infection [S92]. Hemoglobin A1c may be useful, although increased red blood cell turnover in HIV infection may underestimate glycemia [S93]. Because nonalcoholic fatty liver disease occurs in 20%–40% of HIV-infected adults [S68, S94–S97] and is closely linked to obesity, visceral adiposity, and insulin resistance [S98], clinicians should have a low threshold to evaluate unexplained transaminase elevations [S94]. Secondary causes of new onset or worsening weight gain should be considered when relevant, including Cushing's syndrome caused by corticosteroids coadministered with PIs or cobicistat [S99, S100]. In keeping with the screening recommendations above, we strongly recommend blood pressure and glycemic control, smoking cessation, and aspirin and/or statin use in all patients with appropriate risk profiles.

MANAGEMENT OF OBESITY AND LIPOHYPERTROPHY

Lifestyle Changes

Structured exercise with or without dietary intervention reduces abdominal obesity in most studies of HIV-infected persons [S101–S108]. Although no studies directly compare dietary and/or exercise interventions, studies with a dietary component have generally been effective in reducing weight and WC but have not consistently resulted in improved glucose metabolism [S101, S102, S109]. A higher fiber diet has been associated with reduced obesity [S110] but not VAT [S111]. Disproportionate SAT loss with diet or exercise has not been observed, providing reassurance that neither worsens preexisting lipoatrophy. One study found no benefit in adding exercise to a low-fat diet [S104]. Data on the efficacy of resistance versus aerobic training are lacking in this population.

In summary, data are insufficient to support any specific dietary or exercise strategy in patients with HIV and abdominal obesity. Although long-term lifestyle intervention adherence may be low, in persons with generalized or abdominal obesity we recommend ≥30 minutes of moderate-intensity physical activity most days of the week plus caloric restriction to ≥500 kcal/d below usual intake (guided by a nutrition professional) to attain and sustain 5%–10% weight loss [S112]. As in the general population, adjuvant behavioral therapy may by helpful in achieving sustained lifestyle modifications.

Role of ART

As above, initiation of NNRTI-, PI-, and INSTI-based ART is generally associated with SAT and VAT gain, although data are lacking with the newer INSTIs (elvitegravir and dolutegravir). Similarly, randomized switch studies have not shown a benefit of switching from a PI (Table 1).

Medical Interventions

Obesity

For patients without isolated central lipohypertrophy but BMI ≥27 kg/m^2 with comorbidity or BMI >30 kg/m^2 without comorbidity, pharmacologic treatment can be considered in addition to diet, exercise, and behavioral modification. There are 5 medications or medication combinations currently approved in the United States to treat obesity in the general population (Table 2), all of which can lead to clinically significant weight loss (≥5% over 1 year) [S113]. Because not all patients will respond, discontinuation or switch to another agent is recommended after 3 months if ≥5% weight loss has not been achieved [S114]. No agent has emerged as first-line therapy. Choice of medication depends on cost, availability, comorbidities, concomitant medications, and side effects. In the general population, phentermine/topiramate and liraglutide demonstrate the highest probability of achieving significant weight loss, whereas naltrexone/bupropion and liraglutide are associated with the highest rates of discontinuation due to an adverse event [S113]. Potential drug–drug interactions between antiobesity medication and ART are shown in Table 2.

In patients with DM, medications also associated with weight loss, including GLP-1 receptor agonists, should be considered. In patients with CVD or uncontrolled hypertension, sympathomimetics such as phentermine should be avoided [S114].

Lipohypertrophy

Growth Hormone Axis Therapy. Given growth hormone's (GH's) lipolytic effects and the association between reduced GH and increased VAT [32, S115, S116], GH axis therapies have specifically been studied for VAT accumulation in HIV.

Table 1. Objective Changes in Central Fat Following Antiretroviral Therapy Initiation and Switch

Study	Intervention	Subjects (no.)	Duration (wks)	Impact on Fat
Randomized Trials of Initial Therapy				
McComsey et al ACTG 5224s [39]	ATV/r or EFV + ABC/3TC or TDF/FTC	269	96	Greater increase CT VAT area ATV/r (26%) vs EFV (12%); not statistically significant
Martinez et al ATADAR [50]	ATV/r or DRV/r + TDF/FTC	178	96	Greater increase DXA trunk fat ATV/r vs DRV/r; no significant VAT difference
McComsey et al ACTG 5260s [38].	RAL, DRV/r or ATV/r + TDF/FTC	330	96	Similar increase CT VAT area (RAL, 29% DRV/r, 21%; ATV/r, 16%)
Moyle et al [49]. CASTLE	ATV/r or LPV/r + TDF/FTC	224	96	Greater increase DXA trunk fat ATV/r vs LPV/r; no significant VAT difference
Vrouenraets et al [48].	ATV/r or SQV/r + TDF/FTC	86	48	Greater increase DXA trunk fat and VAT ATV/r vs SQV/r; not statistically significant
Switch Studies				
Moyle et al [S167]	PI ->EFV	25	52	CT VAT area decreased 10%
Bickel et al PROTRA1 Study [S168]	PI ->EFV	23	48	No change CT VAT area
Tebas et al [S169]	PI ->NVP	40	24	No significant body composition changes DXA or MRI subset
Moyle et al [S170]	PI ->ABC	27	48	No change CT VAT area
McComsey et al [S171] TARHEEL Study	d4T -> ABC or AZT	118	48	CT VAT area decreased 4%; CT SAT area decreased 32%
Moyle et al [S172]	d4T or AZT-> TDF or ABC	105	104	TDF and ABC modest increases DXA SAT; no significant VAT changes
Tebas et al [S173] ACTG A5110	d4T or AZT-> ABC, LPV/r + NVP or delayed switch	101	48	Both arms: increased CT SAT area and decreased VAT-to-total fat ratio Switch to ABC reduced CT VAT area
Curran et al [S174] SPIRAL-LIP Study	PI/r ->RAL or continued PI/r	74	48	RAL: no significant CT VAT or SAT change PI/r: increased CT total abdominal fat and VAT area
Lake et al [S175] WI-Fat Study	PI or NNRTI -> RAL or delayed switch	37	48	No significant CT SAT or VAT area changes
John et al [S176]	d4T or AZT + 3TC + PI -> AZT + 3TC + ABC or continue current	37	48	Increased DXA SAT; no change in CT VAT area
Stanley et al [S177]	LPV/r ->ATV/r	14	24	Significant decrease in CT VAT area

Abbreviations: 3TC, lamivudine; ABC, abacavir; ACTG, AIDS Clinical Trials Group; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; CT, computed tomography; d4T, stavudine; DRV/r, ritonavir-boosted darunavir; DXA, dual x-ray absorptiometry; EFV, efavirenz; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; MRI, magnetic resonance imaging; NVP, nevirapine; PI/r, ritonavir-boosted protease inhibitor; RAL, raltegravir; SAT, subcutaneous adipose tissue; SQV, saquinavir; TDF, tenofovir disoproxil fumarate; VAT, visceral adipose tissue.

Recombinant human GH (rhGH) at supraphysiologic doses (1–6 mg daily) significantly decreases VAT, with some SAT reduction [S117–S121]. However, most studies demonstrate deleterious effects of rhGH on glucose homeostasis. Indeed, rhGH decreases glucose tolerance even at physiologic levels [S122]. Thus, rhGH was not approved by the US Food and Drug Administration for use in HIV-associated lipodystrophy [S123].

Tesamorelin, a GH-releasing hormone analog, is the only drug approved (in some countries) to reduce excess VAT in treated HIV infection. Tesamorelin increases endogenous pituitary GH release, reducing VAT by approximately 15% within 6 months among HIV-infected patients with baseline WC ≥95 cm for males or ≥94 cm for females [S124–S127]. Approximately two-thirds of patients respond to treatment without decreases in SAT [S127]. Increased fasting glucose may occur in a minority of patients and tends to be transient [S127–S129]. Tesamorelin is administered at a fixed dose of 2 mg subcutaneously daily. It has no known significant interactions with ART.

A limitation of tesamorelin is that VAT quantity returns to baseline, on average, by 6 months after discontinuation [S127]. Measuring WC as a VAT surrogate is recommended after 6 months of treatment, along with assessment of quality of life and lipid levels. Any reduction in WC may represent a meaningful reduction in VAT and should also be interpreted in the context of other factors, including patient well-being, quality of abdominal fat on exam, and change in glucose and lipid parameters. Treatment discontinuation should be considered in patients not achieving WC reduction by 6 months. Tesamorelin should be stopped if significant increases in fasting glucose or HbA1C develop. Although tesamorelin did not worsen glucose in diet-controlled diabetics [S124], it should be used cautiously in patients with diabetes, particularly those with suboptimal glycemic control. Tesamorelin is contraindicated in patients with active malignancy and those who are pregnant or trying to achieve pregnancy. Insulin-like growth factor 1 (IGF-1) levels should be monitored 6 months after initiation, with reduction or discontinuation if IGF-1 levels exceed the upper limit of normal. Injection site reactions require discontinuation in 2%–3% of patients [S124].

Metformin. Metformin improves insulin resistance in HIV-infected individuals with underlying metabolic disease

Table 2. Potential Drug Reactions and Interactions Between Antiretroviral Therapy and Antiobesity Medications

Medication	Maximum Dose[a]	Mechanism of Action	Side Effects	ART Interactions
Orlistat	120 mg TID	Pancreatic/gastric lipase inhibitor	↓ fat-soluble vitamin absorption, steatorrhea, fecal incontinence	**Avoid:** Loss of virologic control reported in patients taking ATV/r or EFV [S178, S179].
Phentermine/Topiramate	7.5 mg/46 mg QD	Norepinephrine releasing agent/ GABA receptor modulation	Insomnia, dry mouth, constipation, paraesthesia, dizziness, dysgeusia	**Caution:** Topiramate is a mild CYP3A4 inducer, but clinical relevance is unlikely [S180].
Lorcaserin	10 mg BID	5HT2c receptor agonist	Headache, nausea, dry mouth, dizziness, fatigue, constipation **Caution if also taking**: SSRI, SNRI/ MAOI, St. John's wort, triptans, buproprion, dextromethorphan	None
Naltrexone/ Bupropion	8 mg/90 mg,2 tabs BID	Dopamine/norepi-nephrine reuptake inhibitor/opioid antagonist	Nausea, constipation, headache, vomiting, dizziness	**Caution**: Bupropion CYP2B6 metabolized [S181]. EFV or RTV use may decrease concentrations. Clinical monitoring and standard bupropion doses recommended.
Liraglutide	3 mg daily	GLP-1 agonist	Nausea, vomiting, pancreatitis	None

Abbreviations: ART, antiretroviral therapy; ATV/r, ritonavir-boosted atazanavir; BID, twice daily; CYP2B6, cytochrome P450 2B6; CYP3A4, cytochrome P450 3A4; EFV, efavirenz; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide-1; MAOI, monoamine oxidase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; QD, once daily; RTV, ritonavir; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TID, three times daily.

[a]Please see prescribing information for specific details including starting dose and dose titration.

[S130–S136], and some studies show lipid [S131, S136–S138] and blood pressure benefits [S134]. Metformin is associated with small decreases in BMI (typically ≤1 kg/m^2) [S131, S134, S135, S137], with proportional reductions in VAT in some, but not all, studies [S133, S134, S136–S139]. Metformin also improves markers of fibrinolysis [S135, S140] and endothelial function [S138] and decreases progression of coronary artery calcium [S130]. Thus, in patients with lipohypertrophy, particularly those with impaired glycemia, we recommend (off-label) consideration of metformin for its potential metabolic and cardiovascular benefits rather than specific (and potentially modest) effects on BMI or VAT. Of note, concomitant dolutegravir administration increases metformin concentrations such that 1000 mg daily of metformin is the maximum recommended dose [S141, S142].

Other Agents. The thiazolidinediones (TZDs) rosiglitazone and pioglitazone improve insulin sensitivity [S133, S138, S143–S146] with no effect or an increase in SAT or VAT [S133, S138, S143–S145, S147]. Thus, we do not recommend TZDs for the treatment of lipohypertrophy. Recombinant human leptin (metreleptin) provides metabolic benefit and VAT reduction in HIV-infected persons with severe lipoatrophy and decreased leptin levels in small studies [S148–S150] but is neither indicated nor approved by the US Food and Drug Administration for the treatment of HIV-associated lipohypertrophy. Physiologic testosterone replacement may be considered for patients with hypogonadism assessed by measuring morning free testosterone with a reliable assay [S151] and may decrease overall fat mass [S152]. However, testosterone has not been shown to decrease VAT in HIV [S152], and lipohypertrophy per se is not an indication for testosterone supplementation in HIV-infected adults.

Surgical Interventions

Obesity

Weight-loss (bariatric) surgery is the most effective treatment for obesity, resulting in an average 60%–70% loss of excess body weight and marked improvements in obesity-related conditions [S153–S155]. There are limited data regarding safety and efficacy in HIV, but in small case series, both Roux-en-Y gastric bypass and vertical sleeve gastrectomy appear to be safe, without changes in virologic control or ART drug concentrations [S156–S160]. However, transient but reversible reductions in tenofovir disoproxil fumarate concentrations were recently reported following vertical sleeve gastrectomy without CD4$^+$ T lymphocyte count or HIV-1 RNA alterations [S161], and a more definitive study of ART pharmacokinetics after bariatric surgery is needed. Bariatric surgery should be considered in persons with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with obesity-related comorbidities that are refractory to serious attempts at lifestyle changes.

Lipohypertrophy

HIV-infected individuals with dorsocervical or anterior cervical fat accumulation and pain and/or functional limitations may be candidates for surgical intervention, including suction-assisted lipectomy and dermolipectomy. Fat accumulation may recur, however, requiring repeat procedures. Large studies are lacking, with case studies reporting recurrence rates from 0%–50% [S162–S166]. Data on the metabolic effects of surgical fat removal are also lacking. To our knowledge, there are no reports of surgical omentectomy in HIV-infected patients.

CONCLUSIONS

Obesity and lipohypertrophy are common disease states in treated HIV infection that may have overlapping pathophysiologies and/or synergistic metabolic consequences. Prevention and treatment of these disease states are critical to the present and future health of HIV-infected persons. Although promising treatment strategies exist, further research is needed to better understand the pathophysiology and optimal treatment of obesity and lipohypertrophy in the modern ART era.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Koethe JR, Jenkins CA, Lau B, et al.; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. AIDS Res Hum Retroviruses **2016**; 32:50–8.
2. Taylor BS, Liang Y, Garduño LS, et al. High risk of obesity and weight gain for HIV-infected uninsured minorities. J Acquir Immune Defic Syndr **2014**; 65:e33–40.
3. Hasse B, Iff M, Ledergerber B, et al. Obesity trends and body mass index changes after starting antiretroviral treatment: The Swiss HIV Cohort Study. Open Forum Infect Dis **2014**; 1:ofu040.
4. Guehi C, Badjé A, Gabillard D, et al. High prevalence of being overweight and obese HIV-infected persons, before and after 24 months on early ART in the ANRS 12136 Temprano Trial. AIDS Res Ther **2016**; 13:12.
5. Finkelstein JL, Gala P, Rochford R, Glesby MJ, Mehta S. HIV/AIDS and lipodystrophy: implications for clinical management in resource-limited settings. J Int AIDS Soc **2015**; 18:19033.
6. Abrahams Z, Levitt N, Lesosky M, Maartens G, Dave J. Changes in body fat distribution on dual-energy x-ray absorptiometry in black South Africans starting first-line antiretroviral therapy. AIDS Patient Care STDS **2016**; 30:455–62.
7. Miller J, Carr A, Emery S, et al. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. HIV Med **2003**; 4:293–301.
8. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med **2017**; 376:254–66.
9. World Health Organization. Obesity and overweight fact sheet. Geneva, Switzerland: World Health Organization, **2016**.
10. Hamdy OUG, Oral EA Obesity practice essentials. Medscape **2016**. Available at: http://emedicine.medscape.com/article/123702-overview?pa=ITuIYPPrdEsfeqaniT9mQiz7JzbM9futrdUUOqoEtFrmSFjbI90%2BSCtY2Q0IJ3K%2Fs7CF3wx2Tu1U792SxywYLg%3D%3D.
11. Robles DTHJ. Lipodystrophy in HIV. Medscape **2016**. Available at: http://emedicine.medscape.com/article/1082199-overview.
12. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. Am J Clin Nutr **2009**; 90:1453–6.
13. Staff MC. Obesity risk factors. **2015**. Available at: http://www.mayoclinic.org/diseases-conditions/obesity/basics/risk-factors/con-20014834.
14. Tchkonia T, Morbeck DE, Von Zglinicki T, et al. Fat tissue, aging, and cellular senescence. Aging Cell **2010**; 9:667–84.
15. Nehra V, Allen JM, Mailing LJ, Kashyap PC, Woods JA. Gut microbiota: modulation of host physiology in obesity. Physiology (Bethesda) **2016**; 31:327–35.
16. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature **2006**; 444:1027–31.
17. Duca FA, Swartz TD, Sakar Y, Covasa M. Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota. PLoS One **2012**; 7:e39748.
18. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes **2007**; 56:1761–72.
19. Trent CM, Blaser MJ. Microbially produced acetate: a "missing link" in understanding obesity? Cell Metab **2016**; 24:9–10.
20. Parekh PJ, Nayi VR, Johnson DA, Vinik AI. The role of gut microflora and the cholinergic anti-inflammatory neuroendocrine system in diabetes mellitus. Front Endocrinol (Lausanne) **2016**; 7:55.
21. Lopes HF, Corrêa-Giannella ML, Consolim-Colombo FM, Egan BM. Visceral adiposity syndrome. Diabetol Metab Syndr **2016**; 8:40.
22. Srinivasa S, Fitch KV, Wong K, et al. RAAS activation is associated with visceral adiposity and insulin resistance among HIV-infected patients. J Clin Endocrinol Metab **2015**; 100:2873–82.
23. Figueroa AL, Takx RA, MacNabb MH, et al. Relationship between measures of adiposity, arterial inflammation, and subsequent cardiovascular events. Circ Cardiovasc Imaging **2016**; 9:e004043.
24. Neeland IJ, Ayers CR, Rohatgi AK, et al. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. Obesity (Silver Spring) **2013**; 21:E439–47.
25. du Plessis J, van Pelt J, Korf H, et al. Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. Gastroenterology **2015**; 149:635–48 e14.
26. Gallego-Escuredo JM, Villarroya J, Domingo P, et al. Differentially altered molecular signature of visceral adipose tissue in HIV-1-associated lipodystrophy. J Acquir Immune Defic Syndr **2013**; 64:142–8.
27. Damouche A, Lazure T, Avettand-Fènoël V, et al. Adipose tissue is a neglected viral reservoir and an inflammatory site during chronic HIV and SIV infection. PLoS Pathog **2015**; 11:e1005153.
28. Vidal F, Domingo P, Villarroya F, et al. Adipogenic/lipid, inflammatory, and mitochondrial parameters in subcutaneous adipose tissue of untreated HIV-1-infected long-term nonprogressors: significant alterations despite low viral burden. J Acquir Immune Defic Syndr **2012**; 61:131–7.
29. Agarwal N, Balasubramanyam A. Viral mechanisms of adipose dysfunction: lessons from HIV-1 Vpr. Adipocyte **2015**; 4:55–9.

30. Torriani M, Srinivasa S, Fitch KV, et al. Dysfunctional subcutaneous fat with reduced dicer and brown adipose tissue gene expression in HIV-infected patients. J Clin Endocrinol Metab **2016**; 101:1225–34.
31. Guaraldi G, Luzi K, Bellistrì GM, et al. CD8 T-cell activation is associated with lipodystrophy and visceral fat accumulation in antiretroviral therapy-treated virologically suppressed HIV-infected patients. J Acquir Immune Defic Syndr **2013**; 64:360–6.
32. Rietschel P, Hadigan C, Corcoran C, et al. Assessment of growth hormone dynamics in human immunodeficiency virus-related lipodystrophy. J Clin Endocrinol Metab **2001**; 86:504–10.
33. Srinivasa S, Fitch KV, Wong K, et al. RAAS activation is associated with visceral adiposity and insulin resistance among HIV-infected patients. J Clin Endocrinol Metab **2015;** 100:2873–82**.**
34. Gérard P. Gut microbiota and obesity. Cell Mol Life Sci **2016**; 73:147–62.
35. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. AIDS **2000**; 14:F25–32.
36. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS **2000**; 14:1309–16.
37. Guaraldi G, Stentarelli C, Zona S, et al. The natural history of HIV-associated lipodystrophy in the changing scenario of HIV infection. HIV Med **2014**; 15:587–94.
38. McComsey GA, Moser C, Currier J, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. Clin Infect Dis **2016**; 62:853–62.
39. McComsey GA, Kitch D, Sax PE, 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.
40. Erlandson KM, Lake JE. Fat matters: understanding the role of adipose tissue in health in HIV infection. Curr HIV/AIDS Rep **2016**; 13:20–30.
41. Caron-Debarle M, Lagathu C, Boccara F, Vigouroux C, Capeau J. HIV-associated lipodystrophy: from fat injury to premature aging. Trends Mol Med **2010**; 16:218–29.
42. Capel E, Auclair M, Caron-Debarle M, Capeau J. Effects of ritonavir-boosted darunavir, atazanavir and lopinavir on adipose functions and insulin sensitivity in murine and human adipocytes. Antivir Ther **2012**; 17:549–56.
43. Béréziat V, Cervera P, Le Dour C, et al.; Lipodystrophy Study Group. LMNA mutations induce a non-inflammatory fibrosis and a brown fat-like dystrophy of enlarged cervical adipose tissue. Am J Pathol **2011**; 179:2443–53.
44. Cereijo R, Gallego-Escuredo JM, Moure R, et al. The molecular signature of HIV-1-associated lipomatosis reveals differential involvement of brown and beige/brite adipocyte cell lineages. PLoS One **2015**; 10:e0136571.
45. Caron-Debarle M, Boccara F, Lagathu C, et al. Adipose tissue as a target of HIV-1 antiretroviral drugs. Potential consequences on metabolic regulations. Curr Pharm Des **2010**; 16:3352–60.
46. Lake JE, Currier JS. Metabolic disease in HIV infection. Lancet Infect Dis **2013**; 13:964–75.
47. Haubrich RH, Riddler SA, DiRienzo AG, et al.; AIDS Clinical Trials Group (ACTG) A5142 Study Team. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS **2009**; 23:1109–18.
48. Vrouenraets SM, Wit FW, Fernandez Garcia E, et al.; BASIC Study Group. Randomized comparison of metabolic and renal effects of saquinavir/r or atazanavir/r plus tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients. HIV Med **2011**; 12:620–31.
49. Moyle GJ, Hardy H, Farajallah A, DeGrosky M, McGrath D. Comparison of body composition changes between atazanavir/ritonavir and lopinavir/ritonavir each in combination with tenofovir/emtricitabine in antiretroviral-naïve patients with HIV-1 infection. Clin Drug Investig **2014**; 34:287–96.
50. Martinez E, Gonzalez-Cordon A, Ferrer E, et al.; ATADAR Study Group. Differential body composition effects of protease inhibitors recommended for initial treatment of HIV infection: a randomized clinical trial. Clin Infect Dis **2015**; 60:811–20.
51. Koethe JR, Jenkins CA, Turner M, et al. Body mass index and the risk of incident noncommunicable diseases after starting antiretroviral therapy. HIV Med **2015**; 16:67–72.
52. Hotamisligil GS. Inflammation and metabolic disorders. Nature **2006**; 444:860–7.
53. Lebovitz HE. The relationship of obesity to the metabolic syndrome. Int J Clin Pract Suppl **2003**; 134:18–27.
54. Mave V, Erlandson KM, Gupte N, et al.; ACTG PEARLS and NWCS 319 Study Team. Inflammation and change in body weight with antiretroviral therapy initiation in a multinational cohort of HIV-infected adults. J Infect Dis **2016**; 214:65–72.
55. Hirigo AT, Tesfaye DY. Influences of gender in metabolic syndrome and its components among people living with HIV virus using antiretroviral treatment in Hawassa, southern Ethiopia. BMC Res Notes **2016**; 9:145.
56. Stambullian M, Feliu MS, Cassetti LI, Slobodianik NH. Nutritional status and lipid profile in HIV-infected adults. Endocr Metab Immune Disord Drug Targets **2015**; 15:302–7.
57. Hulgan T, Boger MS, Liao DH, et al. Urinary eicosanoid metabolites in HIV-infected women with central obesity switching to raltegravir: an analysis from the women, integrase, and fat accumulation trial. Mediators Inflamm **2014**; 2014:803095.
58. Scherzer R, Heymsfield SB, Lee D, et al.; Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection. AIDS **2011**; 25:1405–14.
59. Lake JE, Wohl D, Scherzer R, et al. Regional fat deposition and cardiovascular risk in HIV infection: the FRAM study. AIDS Care **2011**; 23:929–38.
60. Palella FJ Jr, McKibben R, Post WS, et al. anatomic fat depots and coronary plaque among human immunodeficiency virus-infected and uninfected men in the Multicenter AIDS Cohort Study. Open Forum Infect Dis **2016**; 3:ofw098.