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OBESITY AND WEIGHT GAIN IN PERSONS WITH HIV

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Abstract

Purpose of review—The proportion of overweight and obese persons with HIV (PWH) has increased since the introduction of antiretroviral therapy (ART). We aim to summarize recent literature on risks of weight gain, discuss adipose tissue changes in HIV and obesity, and synthesize current understanding of how excess adiposity and HIV contribute to metabolic complications.

Recent findings—Recent studies have implicated contemporary ART regimens, including use of integrase strand transfer inhibitors and tenofovir alafenamide, as a contributor to weight gain, though the mechanisms are unclear. Metabolic dysregulation is linked to ectopic fat and alterations in adipose immune cell populations that accompany HIV and obesity. These factors contribute to an increasing burden of metabolic diseases in the aging HIV population.

Summary—Obesity compounds an increasing burden of metabolic disease among PWH, and understanding the role of fat partitioning and HIV- and ART-related adipose tissue dysfunction may guide prevention and treatment strategies.

Keywords

obesity; HIV; metabolic disease; weight gain; adipose tissue; inflammation

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Conflicts of Interest

Samuel Bailin, Curtis Gabriel, Celestine Wanjalla, and John Koethe declare that they have no conflicts of interest.

Ethics Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Introduction

The prevalence of HIV-associated wasting has declined with the introduction of combination antiretroviral therapy (ART). However, this has been accompanied by an increasing proportion of overweight and obese persons with HIV (PWH) [1–3]. The obesogenic environment of resource rich countries [4, 5], reversal of the catabolic state associated with uncontrolled viremia [6], and direct ART-effects contribute to the changing rates of obesity [7]. While weight gain after initiation of ART is associated with reduced risk of mortality in underweight and normal weight individuals [8], the risk for metabolic diseases including diabetes mellitus, neurocognitive impairment, liver disease, and cardiovascular disease is increased with excess adiposity [9–12]. Furthermore, weight gain in PWH confers greater risk of metabolic disease compared with HIV-negative individuals [9, 11].

Adipose tissue is a large endocrine organ composed of multiple cell types with important functions related to energy storage, metabolism, neuroendocrine signaling, and immunologic regulation [13]. HIV *per se* and ART promote qualitative [14, 15], quantitative [7, 16], and distributive alterations in adipose tissue [17–20]. Both HIV infection and excess adiposity are associated with systemic inflammation that may derive, in part, from changes in the adipose tissue innate and adaptive immune cell profile [21–27]. Together, HIV-specific factors and excess adiposity may explain the excess risk of metabolic diseases in PWH. Here, we review the current epidemiology of obesity and risk factors for weight gain, the current understanding of the role of adipose tissue biology in the development of metabolic diseases, and major complications associated with obesity in PWH (Figure 1).

Epidemiology of Obesity in Person with HIV

The proportion of overweight (body mass index [BMI] 25.0 – 29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) PWH has increased globally. Among PWH in a prospective US Military study, the percentage who were overweight or obese at HIV diagnosis increased from 28% between 1985–1990 to 51% between 1996–2004 [1]. In a multi-cohort analysis of over 14,000 PWH in the United States and Canada, the percentage of obese individuals at ART initiation increased from 9% to 18% between 1998 and 2010 [2]. Furthermore, 22% of individuals with normal BMI became overweight and 18% of overweight individuals became obese within 3 years after ART initiation [2]. Other studies have confirmed high prevalence and incidence of obesity in PWH [3, 28–30], and these changes parallel trends in the general population [31]. Women, minorities, and persons of lower socioeconomic status with HIV carry a disproportionate burden of obesity. Pooled analysis of three randomized clinical trials comparing 760 women with 3,041 men initiating ART found that women had an average BMI increase of 0.59 kg/m^2 higher than men [32]. In a predominantly Hispanic cohort, uninsured minority PWH had a greater prevalence of obesity and greater risk of weight gain compared with Caucasians or insured minorities with HIV [33]. The prevalence of obesity in African American women with HIV is greater than in African American women without HIV in one study [31]. Taken together, obesity prevalence has increased dramatically since the start of the HIV epidemic, with a disproportionate burden among women and minorities.

Anthropometric Parameters

BMI is an anthropometric measurement commonly used in the clinical and research setting, in part due to ease of calculation, high reproducibility, and lack of a need for specialized equipment. Higher BMI is associated with cardiometabolic diseases in the general population including diabetes and cardiovascular disease [34, 35]. However, BMI poorly discriminates between lean body mass and fat body mass, which can be influenced by sex, age, and race/ethnicity [36]. Anthropometric indices of central adiposity estimate the visceral adipose tissue (VAT) compartment and can predict risk of cardiometabolic complications better than BMI [37, 38], particularly in PWH, who more commonly have VAT expansion than HIV-negative individuals with a similar BMI [39, 40]. However, these measurements are imperfect and cannot assess the relative contributions of subcutaneous adipose tissue (SAT) and VAT to waist circumference [41]. Magnetic resonance imaging and computed tomography (CT) remain the gold standard for quantifying SAT and VAT [42], but are principally used for research purposes. Dual-energy X-ray absorptiometry can quantify total trunk fat mass, but software for estimating VAT often provides an underestimate compared to CT imaging in PWH [43]. Recently, CT was used to characterize adipose density as a surrogate marker for adipocyte size and fibrosis in PWH before and after ART [44], but at present adipose tissue biopsy is the standard practice for assessing adipose tissue morphology. In summary, several anthropometric indices are available that characterize adiposity in PWH, but measurements of central adiposity are most strongly associated with risk of metabolic disease. CT imaging offers superior quantification of adipose tissue compartments and is increasingly utilized in research settings.

Risk Factors Associated with Weight Gain in Persons with HIV

Weight gain is common among PWH initiating ART and is associated with reduced mortality for individuals who are initially underweight or normal weight [8]. While a shared obesogenic environment likely explains the similar trends in obesity observed between PWH and the general population [31], the initiation of ART likely contributes to weight gain through a variety of mechanisms. HIV-associated wasting, or the weight loss accompanying advanced $CD4^+$ T cell depletion, is characterized by anorexia secondary to effects of elevated inflammatory markers on the hypothalamus [45], increased basal metabolic requirements that can exceed 30% of baseline during secondary infections [6, 46], and a catabolic state resulting from increased protein turnover [47]. The initiation of ART reverses this catabolic state, reduces circulating inflammatory markers, and can improve appetite and nutrient absorption [48]. Lower baseline $CD4^+$ T cell count and higher HIV RNA viral load are associated with more weight gain after ART initiation [2, 8, 28, 32, 49]. Excess caloric intake, a high-fat diet, and reduced physical activity also promote weight gain and obesity [4, 5].

Many studies have examined the role of ART medications in weight gain among PWH. Older nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have not been associated with differential weight gain [1, 7, 28, 49, 50], but studies of protease inhibitors (PIs) have been mixed. In an ACTG trial, 269 PWH were randomized to an NRTI backbone and either efavirenz (EFV) or atazanavir-

ritonavir (ATV/r), and ATV/r was associated with greater BMI gain with a trend towards increased VAT compared with EFV at 96 weeks [51].

Integrase strand transfer inhibitors (INSTI; e.g., raltegravir [RAL], elvitegravir [EVG], dolutegravir [DTG] and bictegravir [BIC]) are a more recently available class of ART medications with a good tolerability profile and genetic barrier to HIV drug resistance [52, 53]. INSTI-based ART regimens are now the recommended first-line treatment for most PWH [54], but several recent studies, primarily from single sites or cohorts, report greater weight gain among persons receiving INSTI-based ART regimens for initial therapy as compared to PI and NNRTI-based regimens. In a cohort from Brazil, PWH on RAL-based regimens were 7-fold more likely to become obese (BMI ≥ 30 kg/m^2) compared to those receiving NNRTI- or PI-based regimens [49]. In other observational studies, INSTI-based regimens generally, and particularly DTG-based ART regimens [55–58], were associated with greater weight gain.

In the prospective AIDS Clinical Trial Group (ACTG) study A5257, the use of RAL with tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) as an initial ART regimen was associated with greater increases in waist circumference and increased odds of a >10% weight gain at 96 weeks, compared to ART regimens including ritonavir-boosted darunavir or ritonavir-boosted atazanavir, each combined with TDF/FTC [59]. In Cameroon, the NAMSAL study randomized 613 PWH to either tenofovir-lamivudine with DTG or EFV and found that individuals randomized to the DTG-containing regimen gained significantly more weight (5 kg vs 3 kg) at 48 weeks with the most weight gain observed among women [60]. Similarly, a recent pooled analysis of 8 phase III clinical trials involving 5680 ART-naïve participants found that 17.3% of participants had ≥ 10% weight gain from baseline, and weight gain was greater with INSTIs (3.24 kg) compared to NNRTI (1.93 kg) and PI (1.72 kg) [7].

The use of tenofovir alafenamide (TAF), approved in the US in November 2015, is rapidly increasing given the lower incidence of adverse bone and renal effects compared to TDF. Recent data from randomized trials and smaller observational studies indicate that TAF use may predispose to weight gain independent of concomitant INSTI use [16, 61]. In the ADVANCE study, ART-naïve South African women randomized to DTG/TAF/FTC gained an average of 6.4 kg at 48 weeks of treatment, as compared to 3.2 kg on DTG/TDF/FTC and 1.7 kg on EFV/TDF/FTC [16]. For men, weight gain at 48 weeks was 4.7 kg, 3.0 kg, and 0.5 kg, respectively, on the same regimens. Over the 48 weeks, weight continued to increase in both men and women. Similarly, a pooled analysis of randomized controlled clinical trials found higher weight gain over 96 weeks among those starting TAF-containing regiments as compared to other NRTIs. At 96 weeks, mean weight gains by NRTI were: TAF, 4.25 kg; abacavir (ABC), 3.08 kg; TDF, 2.07 kg; and AZT 0.39 kg after adjusting for age, race, sex, baseline clinical factors, and additional agents in the regimen [7].

The mechanisms contributing to weight gain on ART are incompletely understood and could reflect off target effects of the medications or a greater efficacy and suppression of viral reservoirs that reduces the metabolic cost of HIV infection [62]. Several studies are forthcoming that will shed light on whether metabolic abnormalities are independent of

weight gain, whether genetic polymorphisms underlie risk of weight gain, and whether changing to another regimen can reverse weight gain.

Adipose Tissue Distribution and Deposition is Altered in HIV

HIV *per se* and ART medications influence partitioning and distribution of the adipose tissue compartment that can predispose to metabolic complications. As discussed previously, HIV-associated wasting was characterized by anorexia, increased protein turnover, and higher resting energy expenditure, mediated in part by persistent inflammation in the setting of uncontrolled viremia. SAT from untreated PWH demonstrates mitochondrial DNA depletion and reduced function of several enzymes important for aerobic metabolism relative to HIV-negative persons [17]. Viral proteins including HIV viral protein R (Vpr), trans-activator of transcription protein (Tat), and negative regulatory factor (Nef) can mediate changes in adipocyte function through alteration in expression of adiponectin, lipoprotein lipase, glucose transporter type 4 (GLUT4), and peroxisome proliferator-activated receptor gamma [63–65].

Early ART regimens incorporating thymidine analogues affected adipose distribution with lipoatrophy of the face, limbs, and buttocks and lipohypertrophy of visceral, cervical, and dorsocervical areas [18–20, 66, 67]. Importantly, PWH on ART had increased total body fat in the trunk and lower percentage in the limbs compared with HIV-negative despite absence of clinically apparent lipodystrophy [68], and these changes persist even after changing ART [18]. Impaired energy storage in the SAT compartment is hypothesized to result in expansion of VAT and other ectopic adipose deposits [69], which may occur because VAT is less susceptible to toxic effects of ART and HIV than the SAT compartment [70, 71]. Persons with lipodystrophy have a higher rate of total lipolysis as measured using intravenous infusions of stable isotopes of glycerol and palmitate, and increased free fatty acid levels compared with HIV-negative [72]. In addition, PWH have reduced postprandial clearance and storage of plasma triacylglycerols [73], and increased rate of intrahepatic and intra-adipocyte fatty acid reesterfication [74]. Finally, *de novo* hepatic lipogenesis is increased 3 to 4 fold in HIV-associated wasting compared with controls [75]. Taken together, accelerated lipolysis, increased de novo hepatic lipogenesis, and reduced clearance of plasma free fatty acids likely contribute to increased ectopic fat deposition in the liver, epicardium, and skeletal muscle that can increase the risk of metabolic diseases [76–81]. Increases in ectopic adipose tissue compartments may accompany weight gain in PWH [16], though longitudinal studies with CT imaging are needed.

Adipose Tissue is Characterized by Increased Inflammation in HIV and Obesity

The stromal vascular fraction of adipose tissue contains innate and adaptive immune cells that modulate adipocyte energy storage, function, and inflammation. Macrophages accumulate in adipose tissue with progressive weight gain in HIV-negative individuals [22]. In the setting of obesity, both adipocytes and macrophages secrete higher levels of monocyte chemoattractant protein 1 (MCP-1), which drives local proliferation of macrophage populations [24], and the polarization towards an inflammatory subtype (M1) characterized

by higher levels of TNF-α, IL-6, IL-12, IL-23, and inducible nitric oxide synthase [23]. Macrophage-derived cytokines interfere with adipocyte insulin signaling through downregulation of insulin receptor substrate 1, GLUT4, and phosphoinositide 3-kinase p85alpha [82–84]. Studies of macrophages in adipose tissue of PWH are limited and have conflicting results. One study of SAT showed increasing macrophage density and inflammatory cytokines were associated with peripheral lipoatrophy compared with HIV-negative [85]. A different study of gluteal fold adipose tissue from PWH with BMI between 18 and 35 kg/m^2 showed similar macrophage density compared to matched HIV-negative controls but higher IL-6, IL-8, IL-12p40, and MIP-1α [15]. Taken together, macrophage adipose tissue infiltration increases with obesity, but not necessarily with HIV infection.

In contrast to mixed results on macrophage density, several recent studies report a profound shift in adipose tissue T cell profile towards a $CD8^+$ cell predominance in both HIV and simian immunodeficiency virus (SIV, a model of retrovirus infection that approximates HIV) [27, 86, 87], an intriguing finding given the marked $CD8^+$ T cell infiltration in obesity and the higher rates of metabolic disease in PWH [88–91]. SAT $CD8^+$ T cells from PWH demonstrate increased antigen receptor clonality [87], a finding also reported in animal models of obesity [92]. While this finding of increased clonality could refect local T cell expansion, other studies report a lack of Ki-67 expression on SIV-infected macaque adipose tissue $CD8^+$ T cells and high CD57 expression, a marker of senescence or late differentiation and an indicator of reduced replicative capacity, both of which may reflect minimal *in situ* proliferation [93–95]. A recent study found that despite profound $CD8^+$ enrichment in SAT from PWH compared to controls without HIV, the distribution of $CD4^+$ and $CD8^+$ subsets (naïve, central memory, effector memory [T_{EM}], and effector memory RA^+ [T_{EMRA}]) was similar, suggesting the accumulation of $CD8^+$ cells occurs in a relatively stochastic manner, as opposed to accumulation of one broad subset [96]. These findings suggest the changes in adipose tissue gene expression with HIV infection are not due to the preferential accumulation of a specific $CD8^+$ T cell phenotype. Furthermore, the same study found the SAT of diabetic PWH to be markedly enriched for $CD4^+$ T_{EM} and T_{EMRA} cells co-expressing CD57, CX_3CR1, and GPR56, a phenotype reported to have anti-viral specificity, compared to non-diabetic PWH [97–100]. This finding was notable as $CD4^+$ T cells are an important regulator of insulin resistance and tissue inflammation [26], but in PWH they can also serve as a reservoir for HIV persistence, even in virologically suppressed persons [27]. The latent HIV reservoir in adipose tissue $CD4^+$ T cells likely contributes to tissue inflammation and is an important area to consider in HIV cure research.

Obesity Contributes to Comorbidities

Diabetes Mellitus

The estimated incidence of diabetes in PWH ranges between 3.1 and 14 cases per 1000 patient years [21, 88–90, 101]. In one study of men, the incidence of diabetes in PWH was over 4-fold higher than in HIV-negative after adjusting for age and BMI [88]. In addition, the incidence of prediabetes, or individuals who are at risk for developing diabetes, is even higher with an estimated 125 cases per 1000 patient years in a recent meta-analysis [102]. Traditional risk factors for diabetes among PWH shared with the general population include

older age, increasing BMI and central adiposity, family history of diabetes, and African American or Hispanic origin [12, 102–105]. Specific to HIV, lower baseline $CD4^+$ T cell count and older NRTIs and PIs contribute to additional risk of diabetes [88, 103]. Furthermore, the risk of diabetes with weight gain is greater than in HIV-negative individuals [9]; for each 5 pounds of weight gained, the risk of incident diabetes increases 14% in PWH compared with just 8% in HIV-negative individuals [9]. Some of this elevated risk may be related to higher circulating inflammatory markers [21, 106]. In the SMART and ESPRIT clinical trials, higher IL-6 and high-sensitivity c-reactive protein (hsCRP) at enrollment were associated with incident diabetes, and each doubling of IL-6 was associated with around a 30% increased risk [21]. Virological suppression with ART does not completely normalize systemic inflammation [107], and weight gain with ART may further offset reduction in inflammation [108]. Finally, obesity itself is a pro-inflammatory condition, and is associated with increased circulating inflammatory markers in both PWH and HIV-negative [109, 110]. As observed in the general population, diabetic PWH have significantly higher risk of cardiovascular disease, chronic kidney disease, and mortality compared to non-diabetics [105], highlighting the importance of addressing metabolic disease risk factors in the HIV population. However, how obesity mediates excess risk of insulin resistance in PWH is incompletely understood. In one study the prevalence of metabolically healthy obese PWH was similar to the prevalence in obese HIV-negative individuals, but was lower in non-obese PWH compared with non-obese HIV-negative individuals [111]. Another study found that obese PWH had worse cardiovascular parameters but no difference in insulin sensitivity compared with obese HIV-negative individuals [110]. Taken together, obesity in PWH appears to have a greater impact on cardiovascular parameters than insulin resistance and non-traditional risk factors likely have an important role in the development of diabetes.

Neurocognitive Impairment

The prevalence of neurocognitive impairment (NCI) is common in PWH even after the introduction of effective ART, suggesting additional factors aside from viral replication contribute to cognitive dysfunction [112]. In a sub-study of the CHARTER cohort, the prevalence of NCI was 40% and increased central adiposity, as measured by waist circumference, was associated with a higher risk of NCI [10]. Another study confirmed the risk of increased NCI with higher waist circumference, likely mediated through elevated systemic inflammation as reflected by IL-6 and cerebrospinal fluid soluble CD40L (a marker of microglial and macrophage activation) concentrations [113]. Moreover, greater VAT measured by CT was associated with more volume loss of the superior temporal gyrus, insula, and right caudate nucleus and was the strongest predictor of volume changes even after accounting for HIV serostatus [114]. The presence of metabolic disease was independently associated with greater global neurocognitive deficits among PWH, principally the domains of learning, fine motor skills, and executive function, which was not observed among HIV-negative controls [115]. Moreover, diabetes and elevated triglycerides, two aspects of metabolic disease exacerbated by obesity, were strongly associated with increased NCI in the PWH [115]. In summary, evidence suggests that central adiposity and diabetes are major risk factors for NCI among PWH and intervention may prevent or delay cognitive decline.

Cardiovascular Disease

PWH are at increased risk for cardiovascular disease (CVD) including myocardial infarction, stroke, and atherosclerosis [116–119]. In a recent systematic review, the pooled risk ratio for CVD was over 2-fold greater in PWH compared with HIV-negative individuals, and the global burden of CVD in PWH increased between 1990 and 2015 [119]. While traditional risk factors such as male gender, older age, diabetes, hypertension, and race are associated with CVD [117], PWH have elevated risk relative to HIV-negative even after adjusting for demographic characteristics, Framingham risk factors, comorbidities, and viral suppression [120]. ART exposure [116], systemic inflammation [121], reduced arterial elasticity [122], and endothelial dysfunction [123], may contribute to excess risk of CVD in PWH. In the SMART trial, PWH with the highest quartile of IL-6 had a hazard ratio of 4.65 for CVD compared with individuals in the lowest quartile, and this was independent of other predictors of CVD [121]. Central adiposity is associated with other predictors of cardiovascular disease in PWH [39], and ectopic adipose deposition has been associated with CVD in both PWH and HIV-negative [76, 77, 124]. However, the role of obesity, defined solely by BMI, in modifying risk of CVD is unclear. In the D:A:D study, individuals were longitudinally followed and compared to individuals with normal BMI, obese individuals had a 1.31 (confidence interval 1.03–1.67) relative risk of CVD [12]. A recent study compared non-obese and obese PWH and found that while obese individuals had higher levels of circulating inflammatory markers including IL-6, hsCRP, and TNF-α receptor 1, both groups had similar levels of intercellular adhesion molecule 1 and carotid intima-media thickening, suggesting a limited role of adiposity-mediated inflammation in endovascular activation and excess CVD burden [110]. While obesity is a proinflammatory condition and a contributor to hypertension and insulin resistance, important risk factors for CVD, further studies are necessary to understand the relationship of excess adiposity, inflammation, and risk of CVD in PWH.

Liver Disease

Liver disease is the leading cause of non-AIDS related mortality in PWH [125]. PWH carry a disproportionate burden of non-alcoholic fatty liver disease (NAFLD) with an estimated prevalence of 35% [126], compared to 25% in the general population [127]. NAFLD represents a spectrum of disease that ranges from simple steatosis to steatohepatitis to fibrosis, and can eventually lead to hepatic cirrhosis and hepatocellular carcinoma [128]. PWH with NAFLD are more likely to develop steatohepatitis and hepatic fibrosis than HIV-negative persons with NAFLD [129, 130]. In addition, HIV-associated NAFLD is associated with increased risk of extrahepatic disease including diabetes and CVD [131, 132]. Higher BMI is a risk factor for HIV-associated NAFLD and measurements of central adiposity are strongly associated with NAFLD and may be useful as a screening tool [126, 133, 134]. Interestingly, PWH with NAFLD had lower BMI and higher physical activity level compared to HIV-negative patients with NAFLD [11].

PWH have been shown to have increased lipolysis and hepatic re-esterification of fatty acids [72, 74], increased *de novo* lipogenesis [75] and decreased ability to clear very-low-density lipoprotein (VLDL) triglyceride [135]. Furthermore, changes in hepatic expression of PPARgamma and sterol regulatory element-binding protein (SREBP)-1 have been shown to

be associated with steatohepatitis and lipodystrophy in PWH [136]. Exposure to certain ART agents has also been shown to be a risk factor for the development of NAFLD in PWH [137–141]. Collectively, the changes in lipid and glucose metabolism in PLWH lead to increased ectopic lipid deposition in the liver and other tissues which contribute to the activation of inflammatory pathways associated with metabolic dysregulation, inflammation and fibrosis in the liver [128, 142–144].

Weight Loss Interventions

Medical Weight Loss Interventions

Behavioral interventions through caloric restriction and physical exercise are effective in promoting weight loss in PWH, including adipose tissue loss in subcutaneous and visceral compartments [145–152]. These interventions had mixed efficacy on improving metabolic parameters [146, 147], but a recent study evaluating diet-induced weight-loss demonstrated improved insulin sensitivity in women with HIV to the same extent as women without HIV [152]. Several oral agents are FDA approved for weight loss including orlistat, lorcaserin, phentermine-topiramate, liraglutide, and naltrexone-bupropion, but limited data are available on use in PWH. Tesamorelin is a synthetic growth hormone-releasing hormone analogue FDA approved for reduction of central adiposity associated with lipodystrophy that has been shown to reduce VAT and liver fat and may improve metabolic parameters in those who have VAT reduction [153, 154]. As discussed in a previous section, there are currently no studies that have examined if changing ART regimen affects weight gain associated with contemporary ART.

Surgical Weight Loss Interventions

Bariatric surgery remains the most effective intervention for durable weight loss among obese members of the general population, with significant improvement in associated co-morbidities including hypertension, obstructive sleep apnea, diabetes, and hyperlipidemia [155]. VAT loss occurs postoperatively and is greatest in individuals with baseline diabetes [156]. In one study of obese diabetic patients, 50% of those who underwent bariatric surgery maintained diabetes remission at 5 years compared to none in the medical intervention group [157]. Evidence of efficacy is limited in PWH, but retrospective studies suggest surgery is effective and safe [158–160]. A retrospective study of 11 PWH who underwent bariatric surgery matched 1:5 with HIV-negative participants showed a similar reduction in weight and no excess morbidity or mortality [161], and mortality in PWH was not increased after bariatric surgery in a study using a large national database [162]. However, alteration of the gastrointestinal tract could reduce absorption of ART medications. One study of PWH undergoing sleeve gastrectomy assessed pharmacokinetics of ART regimens and found that raltegravir and atazanavir concentrations were below standard values, and 4 individuals had detectable viral loads after surgery, suggesting decreased absorption [163]. In summary, bariatric surgery is an effective intervention for durable weight loss and improvement of co-morbidities, but more studies are required to evaluate potential pharmacokinetic effects.

Conclusions

The prevalence and incidence of obesity in PWH has increased over the past two decades, likely reflective of trends in the population at large, improved survival, and the introduction of new ART agents. The rise in obesity has been accompanied by an increasing burden of metabolic diseases including insulin resistance, neurocognitive impairment, and hepatic disease, though the effects on cardiovascular disease are less clear. Understanding the effects of ART and HIV on fat partitioning and adipose tissue metabolic function may lead to therapeutic interventions that prevent and manage metabolic complications in PWH.

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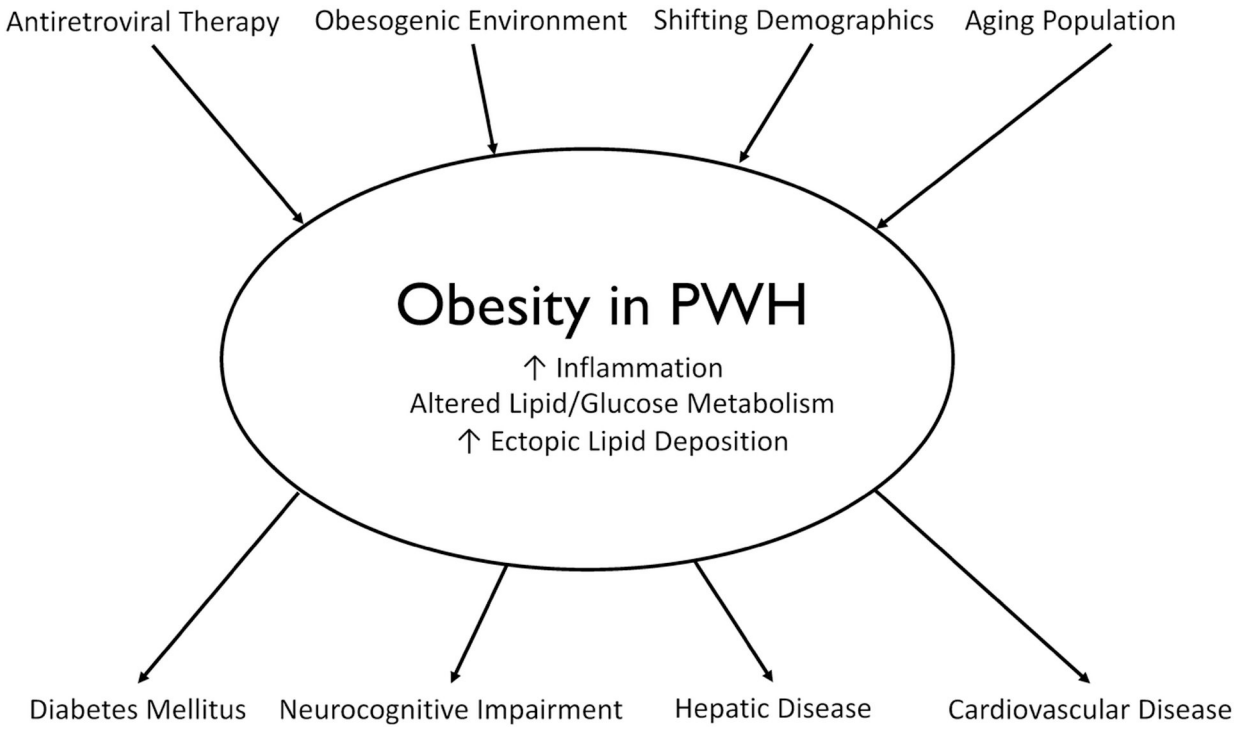

Figure 1.

Proposed model of obesity in persons with HIV (PWH). Contemporary antiretroviral therapy agents (principally integrase strand transfer inhibitors and tenofovir alafenamide), an obesogenic environment (high-fat diet and physical inactivity), shifting demographics, and an aging population predispose to obesity. Obesity in persons with HIV results in increased inflammation, increased ectopic lipid disposition, and alterations in lipid and glucose metabolism. This contributes to metabolic complications including diabetes mellitus, neurocognitive impairment, and hepatic disease. The link between obesity as measured by body mass index and cardiovascular disease is not completely understood.