HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2017 January 02.

Published in final edited form as:

AIDS. 2016 January 2; 30(1): 83–91. doi:10.1097/QAD.0000000000000893.

The Metabolic and Cardiovascular Consequences of Obesity in Persons with HIV on Long-term Antiretroviral Therapy

John R. Koethe, MD, MS[1], **Heather Grome, MD**[2], **Cathy A. Jenkins, MS**[3], **Spyros A. Kalams, MD**[1,4], and **Timothy R. Sterling, MD**[1]

[1]Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee

[2]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

[3]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee

[4]Department of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee

Abstract

Objective—This study assessed the effect of obesity on metabolic and cardiovascular disease risk factors in HIV-infected adults on antiretroviral therapy (ART) with sustained virologic suppression.

Design—Observational, comparative cohort study with three group-matched arms: 35 non-obese and 35 obese HIV-infected persons on efavirenz, tenofovir, and emtricitabine with plasma HIV-1 RNA <50 copies/ml for >2 years, and 30 obese HIV-uninfected controls. Subjects did not have diabetes or known cardiovascular disease.

Methods—We compared glucose tolerance, serum lipids, brachial artery flow mediated dilation (FMD), carotid intima-media thickness (cIMT), and soluble inflammatory and vascular adhesion markers between non-obese and obese HIV-infected subjects, and between obese HIV-infected and HIV-uninfected subjects, using Wilcoxon rank sum tests and multivariate linear regression.

Results—The cohort was 52% male and 48% non-white. Non-obese and obese HIV-infected subjects did not differ by clinical or demographic characteristics. HIV-uninfected obese controls were younger than obese HIV-infected subjects and less likely to smoke ($p \leq 0.03$ for both). Among HIV-infected subjects, obesity was associated with greater insulin release, lower insulin sensitivity, and higher serum hsCRP, IL-6, and TNF-α receptor 1 levels ($p<0.001$), but similar lipid profiles, sCD14, sCD163, ICAM-1 and VCAM-1, and cIMT and FMD. In contrast, HIV-infected subjects had adverse lipid changes, and greater circulating ICAM-1, VCAM-1 and sCD14, compared to HIV-uninfected controls after adjusting for age and other factors.

Conclusions—Obesity impairs glucose metabolism and contributes to circulating hsCRP, IL-6, and TNF-α receptor 1 levels, but has few additive effects on dyslipidemia and endothelial activation, in HIV-infected adults on long-term ART.

Corresponding author and reprint requests: John R. Koethe, MD, Division of Infectious Diseases, Vanderbilt University Medical Center, A2200-MCN, 1161 21st Avenue South, Nashville, TN 37232-2582, USA, Phone: +1 (615) 322-2035, Fax: +1 (615) 343-6160, john.r.koethe@vanderbilt.edu.

Introduction

HIV-infected persons on long-term antiretroviral therapy (ART) are at increased risk of developing cardiovascular and metabolic disease as compared to HIV-uninfected individuals with otherwise similar risk profiles [1–5]. This observation has been attributed to HIV-related factors such as persistent systemic or vascular inflammation [6, 7], antiretroviral toxicity [8, 9], or changes in immune cell populations or function [10, 11]. However, epidemiologic studies have demonstrated heterogeneous effects of non-HIV related risk factors on the incidence of non-communicable diseases (NCDs) in the context of HIV infection. In particular, a higher body mass index (BMI) is associated with an increased risk of an incident diabetes mellitus diagnosis among both HIV-infected and HIV–uninfected persons, but the incremental effect of each unit increase in BMI on diabetes risk is disproportionately greater in HIV-infected persons as compared to HIV-uninfected persons [5, 8, 12]. In contrast, large epidemiologic studies have not found that a higher BMI increases the risk of incident cardiovascular events in HIV-infected persons [3, 4, 13]. Interpreting these findings on BMI and NCD incidence in the HIV-infected population is hampered by a paucity of clinical data on how body composition and ART-treated HIV infection interact to affect metabolic and cardiovascular parameters.

The prevalence of obesity (a BMI >30 kg/m^2) among HIV-infected individuals in the United States is approaching parity with the general population and is particularly high among women and minorities [14–18]. As patients can now survive decades on ART, the identification of individuals at high risk for developing chronic comorbid medical conditions is increasingly important for clinical care. In this study we use a comparative cohort approach to first assess how obesity affects glucose tolerance, lipid profiles, vascular health, and systemic inflammation in HIV-infected adults on stable, long-term ART treatment, and second to assess how the presence of treated HIV-infection affects the same outcomes in obese individuals.

Methods

We enrolled 70 HIV-infected patients on ART from the Vanderbilt Comprehensive Care Clinic and 30 obese (BMI >30 kg/m^2), uninfected controls between April 2013 and September 2014. The HIV-infected subjects were distributed equally between four BMI categories of <25.0, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2. Within each BMI strata similar numbers of males and females and whites and non-whites were enrolled. All subjects were on efavirenz, tenofovir, and emtricitabine (i.e., the combination pill *Atripla*) for at least the 6 months prior to enrollment and had been on ART treatment with persistent HIV-1 RNA measurements <50 copies/ml for at least the previous 2 years. Additional inclusion criteria were CD4+ count >350 cells/μl at the time of enrollment, no use of any anti-diabetic or statin (i.e., HMG CoA reductase inhibitor) medication in the prior 6 months, no self-reported heavy alcohol (defined as >11 drinks/week) or cocaine/amphetamine use, no active infectious conditions aside from HIV, and no previously diagnosed diabetes, cardiovascular disease (CVD), or rheumatologic disease recorded in the medical record.

Thirty healthy volunteers with obesity were recruited from the community to serve as controls. Controls were distributed equally between the BMI categories of 30.0–34.5 and >35 kg/m^2 and group matched by sex and race with the HIV-infected subjects. The uninfected controls had not received any anti-diabetic or statin medications in the prior 6 months, did not report alcohol or illicit drug abuse, and had no active infectious conditions or previously diagnosed diabetes, CVD, or rheumatologic disease by self-report.

Data on ART history and CD4+ count and viral load values were obtained from the medical record. Data on smoking was obtained by self report. All 100 subjects underwent a 3-hour assessment in the Vanderbilt Clinical Research Center after fasting overnight for at least 8 hours (all visits began between 8 and 11 am). Brachial artery reactive hyperemia and bilateral carotid intima-media thickness (IMT) was measured using a Philips iE33 ultrasound with L9–3 linear transducer prior to any other procedures. A 3-lead ECG was attached to chest in standard manner and the patient relaxed in a supine position for 10 minutes. A blood pressure cuff was placed on the right forearm 1cm below the antecubital fossa and the arm was extended away from body 90 degrees resting on an armboard at the height of the bed. An image of the brachial artery 3–10 cm above the antecubital fossa was acquired on the EKG “R” wave to measure the artery diameter. The cuff was inflated to 50 mmHg above systolic pressure for 5 minutes. After deflation, EKG-gated measurements were acquired from still-frame images at 30 seconds, 60 seconds, 90 seconds and 120 seconds. The flow mediated dilation (FMD) was calculated as the largest percent increase in vessel diameter after cuff deflation.

Right common carotid artery (CCA) and carotid bulb images were acquired using EKG gating after patients were placed supine on the bed without a pillow and with the head turned 45 degrees to the left. The IMT was measured in plaque free arterial segments at the carotid bulb, and 1 cm from the bulb, as the distance between the inner echogenic line representing the blood-intima interface and the outer echogenic line representing the media-adventia border. A similar procedure was used for measurement of the proximal internal carotid artery (ICA) IMT at 1 cm, and all measurements were repeated on the left side of the head (in this analysis, we report IMT values from the right side only).

After ultrasound assessments were complete, fasting blood samples were collected. High-sensitivity C-reactive protein (hsCRP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and glucose were measured by the Vanderbilt Clinical Chemistry Laboratory. Plasma levels of soluble CD14 and CD163, two surface markers released into circulation by activated macrophages, were measured using ELISA (R&D Systems, Minneapolis, MN). Serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) receptor 1, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) were measured in duplicate using a multiple immunoassay (MesoScale, Rockville, MD). Fasting insulin was measured by radioimmunoassay.

After the collection of the fasting blood sample, subjects ingested a 75 gram oral glucose dose dissolved in 12 ounces of water. Plasma glucose was again measured at 90 and 120 minutes, and insulin at 90 minutes. Fasting beta cell function and insulin sensitivity were calculated using the Homeostasis Model Assessment 2 (HOMA2) equation (https://

www.dtu.ox.ac.uk/homacalculator) [19]. The oral glucose insulin sensitivity [OGIS] index (a model developed to approximate a glucose clamp study) was calculated using fasting, 90 minute, and 120 minute glucose and insulin values [20].

Anthropometric measurements were performed in triplicate and averaged. A full body dual-energy x-ray absorptiometry (DEXA) scan was performed on all subjects to measure regional and total bone mass, lean mass, and fat mass (GE Lunar Prodigy). A software algorithm estimated visceral fat mass.

Statistical analyses

Demographic, clinical, and body composition characteristics were compared in a pairwise fashion by obesity status in the HIV infected group, and by HIV status in the obese group using Wilcoxon rank sum or chi-square tests. Medians and interquartile ranges were calculated for continuous variables and percentages for categorical variables.

To assess whether obesity alters metabolic and cardiovascular parameters in the context of long-term, treated HIV infection, we compared each outcome variable according to obesity status in the HIV-infected participants using Wilcoxon Rank Sum tests. A secondary analysis using multivariable linear regression was also performed to assess the relationship of DEXA percentage body fat with each outcome variable after adjusting for age, sex, race, CD4+ count, current smoking status, and the duration of ART treatment. DEXA percent body fat was used rather than BMI as it represents a more accurate measurement of total adiposity and, unlike DEXA total body fat, it is less affected by differences in height. The outcome variables were natural log transformed and CD4+ count was square root transformed. Sensitivity analyses adjusted for hepatitis C co-infection and pre-treatment CD4+ count.

To assess whether HIV status affected metabolic and cardiovascular parameters in the context of obesity, we limited our analysis to the 35 obese HIV-infected and 30 obese HIV-uninfected subjects and utilized multivariable linear regression models incorporating HIV status, age, sex, race, smoking status, DEXA body fat, and an interaction term between HIV and body fat. The outcome variables were natural log transformed. In models where the interaction term p-value was >0.1, the regression coefficient for HIV status was calculated after removing the interaction term from the model. Sensitivity analyses were performed which adjusted for hepatitis C co-infection and pre-treatment CD4+ count.

The selected metabolic and cardiovascular outcome variables were grouped into biologically rational categories (glucose metabolism, adipokines, plasma lipids, inflammation biomarkers, vascular adhesion biomarkers, and vascular ultrasound measurements) and represented planned comparisons. The analysis strategy was to assess the probability of an association between the exposure variable and members of each category, and no adjustments were made for multiple comparisons [21]. Analyses were conducted using SPSS 22.0.0 (IBM) and R Statistical Software (http://www.R-project.org).

Results

Comparison of HIV-infected Subjects by Obesity Status

The clinical and demographic characteristics of the HIV-infected subjects stratified by obesity status are shown in Table 1. Age, race, sex, smoking status, CD4+ count at enrollment and ART initiation, duration of ART treatment, and hepatitis C prevalence were similar between the HIV-infected non-obese and obese ($p>0.05$ for all comparisons).

Among the HIV-infected subjects, obesity was associated with increased HOMA 2 model β-cell insulin release, and lower HOMA 2 and OGIS 120 index insulin sensitivity (Table 2; $p\leq0.001$ for all). There was no significant difference in percent glycosolated hemoglobin, which likely reflects compensation from the over 2-fold higher median fasting insulin levels in the obese ($p<0.001$). Obesity was closely associated with higher serum hsCRP, IL-6, and TNF-α receptor 1 levels ($p<0.001$), but not soluble CD14 or CD163. We observed no difference between obese and non-obese HIV-infected subjects in median plasma lipid levels, ICAM-1 and VCAM-1 levels, or measurements of carotid IMT or brachial artery FMD. Similarly, in the adjusted linear regression model, DEXA percent fat mass was associated with insulin resistance and hsCRP, IL-6, and TNF-α receptor 1 levels, but not plasma lipids, vascular adhesion molecules, or vascular ultrasound measurements (Table 3). These results were similar when the model was further adjusted for hepatitis C and pre-treatment CD4+ count (data not shown).

Comparison of Obese Subjects by HIV Status

The clinical and demographic characteristics of the obese subjects stratified by HIV status are shown in Table 4. The obese HIV-infected had a higher median age compared to the obese controls, 46 versus 37 years ($p=0.01$), and a higher smoking and hepatitis C prevalence, but did not significantly differ according to sex or race, or total bone mass, lean mass, or fat mass. However, obese HIV+ subjects had a higher trunk-to-appendicular fat ratio, a predictor of cardiovascular disease, compared to controls (1.58 versus 1.32; $p=0.05$) and higher calculated visceral fat (1.97 versus 1.60 kg, $p=0.04$).

In contrast to the metabolic findings in the HIV-infected subjects, HIV status was found to be associated with adverse changes in lipid profiles and higher soluble endothelial adhesion molecules in obese subjects in a regression model adjusted for age and other covariates (Table 5). HIV status was associated with higher total cholesterol, LDL, and triglycerides, and lower HDL, and higher plasma ICAM-1 and VCAM-1. HIV-infected subjects also had significantly higher sCD14, a marker of monocyte activation. We observed no significant differences in β-cell insulin release, insulin sensitivity, serum hsCRP, IL-6, TNF-α receptor 1, or sCD163 levels, or ultrasound measurements of carotid IMT or brachial artery FMD. These results were similar when the model was further adjusted for hepatitis C co-infection.

The absolute values of the cardiovascular and metabolic parameters in obese HIV+ subjects and obese controls are compared using Wilcoxon rank sum tests in the Supplementary Table. The variables which differ significantly according to HIV status are similar to the adjusted regression model with the exception of lipids, which we attribute to the lack of adjustment for age and smoking.

Discussion

In HIV-infected adults on long-term, non-protease inhibitor-based ART and without previously diagnosed metabolic disease or CVD, obesity was associated with increased insulin resistance and systemic inflammation, but obesity did not appear to adversely affect HbA1c or key cardiovascular risk factors including lipid profiles, circulating vascular endothelial adhesion molecules, or measurements of carotid IMT or brachial artery reactivity. Of note, the greater serum insulin levels and calculated insulin resistance in our obese HIV-infected subjects was not accompanied by higher HbA1c values. This indicates an ability to compensate for insulin resistance with greater insulin secretion to maintain glucose homeostasis, but represents a condition more likely to progress to clinical diabetes.

Among obese subjects with similar total and regional adiposity, HIV infection was not associated with significant differences in insulin secretion, calculated insulin resistance, or plasma inflammatory markers (except soluble CD14), but HIV status was associated with adverse changes in plasma lipids and vascular adhesion molecules. We interpret our findings as an indication that greater adipose tissue stores contribute to insulin resistance and circulating cytokines in HIV-infected persons on ART, but any additive effects of obesity on changes in lipids or ICAM-1 and VCAM-1 in HIV-infected persons is masked by the adverse effects of HIV infection alone on these parameters.

Glucose metabolism

Our finding that progressive adiposity is accompanied by lower glucose tolerance in HIV patients is consistent with prior epidemiologic analyses of diabetes in this population. In a multi-country study of 33,000 subjects in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort, a BMI >30 kg/m^2 was associated with a 4.5-fold higher risk of incident diabetes compared to those with a BMI 18–26 kg/m^2, which was independent of cumulative exposure to stavudine, zidovudine, didanosine, and other ART agents known to cause alterations in fat partitioning and adipocyte energy metabolism [8]. A longitudinal study of 1046 HIV-infected French adults found the incidence of diabetes rose in a stepwise fashion with higher BMI strata, again independent of exposure to individual ART medications [12].

While prior studies have reported HIV-infected patients to have significantly higher rates of incident diabetes compared HIV-uninfected persons, we did not observe an association between HIV status and glucose metabolism in the obese subjects [2, 5]. We attribute this to two factors. First, many of the prior studies included patients with substantial cumulative exposure to older ART agents, such as stavudine and zidovudine, which are associated with greater glucose intolerance as compared to newer regimens [2, 8]. Second, we postulate that among our obese subjects the effects of excess adiposity on glucose metabolism may have masked any impact from HIV infection or our selected ART regimen. Prior studies have shown efavirenz treatment is associated with higher blood glucose levels, and a difference in glucose tolerance may have been apparent if we had compared non-obese HIV-infected to non-obese uninfected persons [22, 23].

Lipid profiles and vascular health

We did not observe an adverse impact of obesity on plasma lipids, ICAM-1 or VCAM-1, or ultrasound measurements of carotid IMT or brachial FMD in the HIV-infected subjects. In contrast, a recent study of HIV-infected young women in the Adolescent Trials Network found dyslipidemia was more prevalent at higher BMI, though the median age of subjects was approximately 20 years younger than our cohort [24]. However, our results were in accordance with prior clinical studies showing BMI is not associated with carotid IMT or brachial artery FMD [25, 26]. Our finding that obesity does not adversely affect several clinical risk factors for cardiovascular events is in accordance with large epidemiology studies which found no increased risk of myocardial infarction among higher BMI patients [4, 13].

In contrast, we found treated HIV infection was associated with adverse changes in plasma lipid profiles and endothelial activation, but not carotid IMT or brachial artery FMD, in our obese subjects after adjusting for age and other covariates. HIV infection, despite effective virologic suppression, is an independent risk factor for myocardial infarction and other CVD events, which has been linked to adverse effects on lipid profiles, platelet activation, inflammation, and endothelial function [3, 4]. We observed higher total cholesterol, LDL, and triglycerides, and lower HDL, in the obese HIV-infected subjects compared to HIV-uninfected, but the relative contributions of efavirenz exposure, which is shown to cause more lipid elevations compared to other ART agents, versus HIV infection to these findings deserves further investigation [27–30]. Higher plasma levels of VCAM-1 and ICAM-1 were also associated with HIV infection, which has been reported in prior studies of HIV patients and can persist for years despite effective ART treatment [31–33]. The lack of an association between HIV status and carotid IMT may have been due to our considerably smaller sample size as compared to prior studies [25, 26, 34].

Biomarkers of systemic inflammation

Several markers of systemic inflammation were significantly associated with obesity, but among the obese patients, hsCRP, IL-6, and TNF-α receptor 1 levels did not differ by HIV status. This was unexpected, and we postulate that adipocyte-derived IL-6 and TNF-α masked additional innate immune system activation due to HIV infection. Circulating hsCRP, IL-6, and TNF-α receptor 1 increased with total fat mass, and higher plasma levels of these biomarkers in obese HIV patients have been previously reported by our group and others [35, 36]. We postulate this finding reflects constitutive cytokine production by hypertrophied adipocytes and adipose-resident immune cells (primarily macrophages and, to a lesser extent, lymphocytes) as reported from *in vitro* studies [37–40]. Increased adipose tissue mass is primarily due to adipocyte hypertrophy rather than hyperplasia, and interval increases in adipocyte size result in disproportionate increases in IL-6 and TNF-α expression [37–39]; it is estimated that adipose tissue-derived IL-6 constitutes up to 35% of circulating levels in obese individuals and serves as a major signaling pathway for CRP production [40].

Our findings raise the question of whether hsCRP and IL-6 levels can reliably predict adverse CVD outcomes and mortality as described in prior studies of predominantly non-

obese populations [6, 41, 42]. The link between soluble inflammatory biomarkers and adverse health outcomes reported in prior studies likely reflects the production of these cytokines at sites of tissue inflammation and damage. However, it is unclear whether the same cytokines originating from adipocytes, particularly IL-6 and TNF-α, would contribute substantially to these end-organ pathogenic processes. Of note, sCD14, a soluble monocyte receptor not produced by adipocytes, was significantly higher in our subjects with HIV and did not appear to be affected by fat mass [43]. Higher circulating sCD14 is associated with mortality and disease progression in HIV patients, and may have more utility for predicting health outcomes among obese patients than adipocyte-derived cytokines [44, 45].

Strengths of this study included a uniform ART treatment regimen in all HIV-infected subjects, the exclusion of subjects on medications to treat metabolic or cardiovascular diseases (aside from antihypertensives), a minimum 2-year period of virologic suppression to allow the effects of plasma viremia to fade, a required minimum CD4+ T-cell count (>350 CD4+ cells/μl), and approximately equal distribution of subjects by sex and race (white and non-white). Obese control subjects were matched to HIV-infected subjects by age, race and BMI, and met the same criteria for excluded medications.

While the study sample size was relatively small, we observed several statistically significant findings between the HIV-infected groups and the obese groups which were relatively consistent within each category (e.g., glucose metabolism, lipids, and inflammatory cytokines). This suggests the lack of a detectable difference, when present, was not clearly due to inadequate power. The sample size was calculated to provide 90% power to detect an association between body composition and serum IL-6 levels (based on previously reported cytokine levels in a similar cohort) [35], and 80% power to detect a 37% difference in IL-6 levels between obese HIV-infected and –uninfected subjects. Second, the use of DEXA imaging provided less accurate quantification of visceral fat than CT or MRI. Third, the cross-sectional design prevented assessments of causality or variability of our endpoints over time. Fourth, the age of the HIV-uninfected controls was lower than obese HIV-infected subjects, which precluded direct comparisons of the groups and necessitated the use of multivariable models. Lastly, the regimen of efavirenz, tenofovir, and emtricitabine was selected due to the lower reported effects on lipid parameters and the widespread use if this regimen in the US and worldwide, but additional studies are needed before extrapolating our results to patients on a protease inhibitor or the increasingly common integrase inhibitors.

The health outcomes of obese HIV-infected individuals are increasingly relevant to clinical care as the prevalence of obesity in the HIV population approaches parity with the general population in many areas of the United States and Europe [14–18, 46]. Long-term weight loss maintenance is a major challenge for overweight and obese persons, and in HIV-infected individuals glucose and lipid abnormalities may persist despite short-term weight loss programs [47, 48]. While further long-term data are needed on the reversibility of obesity-associated cardiometabolic risk-factors after weight loss, our findings suggest that the prevention of excessive weight gain and obesity is critical to preventing insulin resistance in HIV patients, while CVD risk reduction remains important for all HIV-infected individuals irrespective of body composition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the participants in the *Adiposity and Immune Activation Cohort* study.

Funding support:

This work was supported by NIAID [grant numbers K23 100700 and K24 AI65298], the NIH-funded Vanderbilt Clinical and Translational Science award from NCRR/NIH [grant number UL1 RR024975-01], and the NIH-funded Tennessee Center for AIDS Research [grant number P30 AI110527]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Table 1

Clinical characteristics and body composition of non-obese and obese HIV-infected subjects

Variable	Non-obese (n=35)	Obese (n=35)	p-value
Age, median years (IQR)	45 (38, 49)	46 (39, 51)	0.61
Female, %	14 (40%)	16 (46%)	0.41
Non-white, %	18 (51%)	20 (57%)	0.63
BMI, median kg/m^2	23.9 (21.9, 26.5)	35.6 (33.0, 40.1)	**<0.001**
Smoker, %	12 (34%)	13 (37%)	0.80
Hepatitis C, %	4 (11%)	4 (11%)	NA
CD4 at enrollment, cells/μl	621 (504, 924)	758 (605, 966)	0.08
CD4% at enrollment	36 (30, 40)	38 (32, 42)	0.15
CD4 at ART initiation, cells/μl	250 (142, 307)	262 (132, 400)	0.59
Duration of ART treatment, years	6.05 (4.33, 9.88)	6.65 (4.42, 11.15)	0.58
DEXA body composition measurements			
Bone mass, kg	2.73 (2.21, 3.07)	2.93 (2.54, 3.39)	**0.03**
Total lean mass, kg	48. 4 (41.0, 55.4)	56.2 (48.9, 65.9)	**<0.001**
Fat mass, kg	21.2 (14.8, 27.7)	46.4 (37.9, 52.2)	**<0.001**

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DEXA, dual-energy x-ray absorptiometry; IQR, interquartile range

Table 2

Comparison of metabolic and cardiovascular parameters between non-obese and obese HIV-infected subjects

Outcome variable	Non-obese (n=35)	Obese (n=35)	p-value
Glucose metabolism assessments			
HOMA2 beta-cell function, %	100 (80, 128)	173 (116, 211)	**<0.001**
HOMA2 insulin sensitivity, %	130 (74, 191)	58 (41, 89)	**<0.001**
OGIS 120, ml/min/m^2	447 (401, 485)	379 (328, 422)	**<0.001**
Hemoglobin A1c, %	5.1 (4.9, 5.5)	5.2 (5.0, 5.6)	0.14
Insulin, µU/ml	6.1 (4.2, 10.6)	13.3 (8.6, 19.4)	**<0.001**
Adipokine levels			
Leptin, ng/ml	9.2 (3.9, 13.4)	30.4 (18.3, 42.6)	**<0.001**
Adiponectin, µg/ml	12.4 (6.7, 16.5)	9.1 (5.2, 12.0)	**0.03**
Resistin, ng/ml	17.5 (11.8, 23.3)	20.0 (14.6, 26.2)	0.28
Plasma lipids			
Total cholesterol, mg/dl	174 (152, 203)	177 (155, 200)	0.59
HDL, mg/dl	46 (35, 64)	44 (39, 49)	0.28
LDL, mg/dl	101 (85, 122)	111 (88, 129)	0.50
Triglycerides, mg/dl	94 (66, 131)	104 (85, 152)	0.12
Inflammation biomarkers			
High sensitivity C-reactive protein, mg/l	1.6 (0.7, 2.8)	5.8 (2.0, 9.4)	**<0.001**
Interleukin-6, pg/ml	2.5 (1.6, 3.8)	4.2 (2.9, 7.1)	**<0.001**
Tumor necrosis factor-alpha receptor 1, ng/ml	11.0 (9.5, 12.2)	12.2 (10.2, 15.1)	**0.048**
Soluble CD163, ng/ml	500 (413, 743)	563 (417, 664)	0.36
Soluble CD14, µg/ml	1.69 (1.44, 2.00)	1.69 (1.50, 1.92)	0.74
Vascular adhesion biomarkers			
Intercellular adhesion molecule 1, ng/ml	513 (441, 663)	557 (448, 617)	0.55
Vascular cell adhesion molecule 1, ng/ml	583 (449, 630)	587 (470, 665)	0.83
Vascular ultrasound measurements			
Carotid bulb intima-media thickness (IMT), cm	0.062 (0.054, 0.069)	0.062 (0.057, 0.077)	0.25
Common carotid IMT, cm	0.057 (0.052, 0.062)	0.062 (0.052, 0.071)	0.11
Internal carotid IMT, cm	0.056 (0.047, 0.067)	0.053 (0.044, 0.071)	0.97
Brachial artery flow-mediated dilation, %	9.0 (5.9, 11.6)	8.4 (4.8, 10.6)	0.31

Abbreviations: HLD, high-density lipoprotein; HOMA, Homeostasis Model Assessment; OGIS, oral glucose insulin sensitivity; LDL, low-density lipoprotein

Table 3

Multivariable linear regression model for the effect of fat mass on metabolic and cardiovascular parameters among HIV-infected subjects on long-term ART (n=70)

Outcome variable	Regression coefficient for percent body fat	p-value
Glucose metabolism assessments		
HOMA2 beta-cell function	0.54	**<0.001**
HOMA2 insulin sensitivity	−0.81	**<0.001**
OGIS 120	−0.48	**0.001**
Hemoglobin A1c	0.10	0.49
Insulin	0.79	**<0.001**
Adipokine levels		
Leptin	0.96	**<0.001**
Adiponectin	−0.21	0.13
Resistin	0.30	0.08
Plasma lipids		
Fasting total cholesterol	0.20	0.22
Fasting HDL	−0.19	0.18
Fasting LDL	0.31	0.05
Fasting triglycerides	0.26	0.09
Inflammation biomarkers		
High sensitivity C-reactive protein, mg/l	0.53	**<0.001**
Interleukin-6, pg/ml	0.45	**0.001**
Tumor necrosis factor-alpha receptor 1, ng/ml	0.32	**0.01**
Soluble CD163	0.24	0.13
Soluble CD14	−0.12	0.42
Vascular adhesion biomarkers		
Intercellular adhesion molecule 1 (ICAM-1), ng/ml	0.09	0.52
Vascular cell adhesion molecule 1 (VCAM-1), ng/ml	0.08	0.57
Vascular ultrasound measurements		
Carotid bulb intima-media thickness (IMT)	0.26	0.08
Common carotid IMT	0.19	0.24
Internal carotid IMT	0.07	0.68
Brachial artery flow-mediated dilation	−0.13	0.41

Multivariable model adjusted for age, sex, race, CD4 count (square root transformed), duration of ART treatment, smoking, and DEXA percent fat

Abbreviations: ART, antiretroviral therapy; DEXA, dual-energy x-ray absorptiometry; HLD, high-density lipoprotein; HOMA, Homeostasis Model Assessment; OGIS, oral glucose insulin sensitivity; LDL, low-density lipoprotein

Table 4

Clinical characteristics and body composition in obese HIV-infected subjects versus obese controls

	Obese HIV-infected (n=35)	Obese HIV uninfected controls (n=30)	p-value
Age, median years (IQR)	46 (39, 51)	37 (28, 44)	**0.01**
Female, %	16 (46%)	18 (60%)	0.25
Non-white, %	20 (57%)	11 (37%)	0.10
BMI, median kg/m^2	35.6 (33.0, 40.1)	35.8 (31.3, 41.0)	0.49
Smoker, %	13 (37%)	4 (13%)	**0.03**
Hepatitis C, %	4 (11%)	0	0.06
Anthropometric measurements			
Waist circumference, cm	122 (109, 130)	114 (99, 129)	0.80
Waist-to-hip ratio	1.01 (0.95, 1.06)	0.94 (0.83, 1.03)	0.24
DEXA body composition measurements			
Bone mass, kg	2.93 (2.54, 3.39)	3.05 (2.66, 3.52)	0.73
Total lean mass, kg	56.2 (48.9, 65.9)	57.0 (46.1, 70.0)	0.93
Fat mass, kg	46.4 (37.9, 52.2)	44.1 (36.0, 53.0)	0.78
Fat mass %	42.7 (37.4, 48.5)	42.0 (38.9, 47.1)	0.67
Limb fat mass, kg	16.7 (14.4, 20.7)	18.4 (14.9, 22.7)	0.31
Limb fat %	16.2 (12.3, 19.8)	17.5 (14.8, 21.2)	0.24
Trunk fat mass, kg	27.1 (22.3, 31.9)	24.8 (19.4, 32.2)	0.25
Trunk fat %	25.6 (21.5, 28.5)	23.7 (20.7, 26.5)	0.12
Trunk-to-appendicular fat ratio	1.58 (1.40, 1.99)	1.32 (1.03, 1.75)	0.05
Calculated visceral fat, kg*	1.97 (1.51, 2.91)	1.60 (0.94, 2.74)	**0.04**

Abbreviations: BMI, body mass index; DEXA, dual-energy x-ray absorptiometry; IQR, interquartile range

*Calculated from DEXA scan data by GE Lunar Prodigy software

Table 5

Relationship of HIV status to metabolic and cardiovascular parameters among obese subjects (35 HIV-infected, 30 HIV-uninfected)

Outcome variable	Regression coefficient for HIV status*	p-value
Glucose metabolism assessments		
HOMA2 beta-cell function	−0.04	0.79
HOMA2 insulin sensitivity	0.13	0.31
OGIS 120	−0.06	0.69
Hemoglobin A1c	−0.16	0.21
Insulin	−0.12	0.34
Adipokine levels		
Leptin	−0.08	0.35
Adiponectin	−0.01	0.96
Resistin	−0.40	**0.004**
Plasma lipids		
Total cholesterol	0.11	**0.03**
HDL	−0.13	**0.04**
LDL	0.08	**<0.01**
Triglycerides	0.20	**0.03**
Inflammation biomarkers		
High sensitivity C-reactive protein, mg/l	−0.01	0.92
Interleukin-6, pg/ml	0.04	0.70
Tumor necrosis factor-alpha receptor 1, ng/ml	0.03	0.81
Soluble CD163	0.13	0.33
Soluble CD14	0.54	**<0.01**
Vascular adhesion biomarkers		
Intercellular adhesion molecule 1 (ICAM-1), ng/ml	0.33	**0.01**
Vascular cell adhesion molecule 1 (VCAM-1), ng/ml	0.31	**0.02**
Vascular ultrasound measurements		
Carotid bulb intima-media thickness (IMT)	−0.09	0.42
Common carotid IMT	−0.04	0.74
Internal carotid IMT	−0.18	0.19
Brachial artery flow-mediated dilation	0.05	0.76

Multivariable model adjusted for age, sex, race, HIV status, smoking status, DEXA total fat mass, and interaction term for DEXA fat mass and HIV status

* In models where the interaction term p-value was >0.1, the regression coefficient for HIV status is calculated after removing the interaction term from the model

Abbreviations: DEXA, dual-energy x-ray absorptiometry; HLD, high-density lipoprotein; HOMA, Homeostasis Model Assessment; OGIS, oral glucose insulin sensitivity; LDL, low-density lipoprotein