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Adipokines, Weight Gain and Metabolic and Inflammatory Markers After Antiretroviral Therapy Initiation: AIDS Clinical Trials Group (ACTG) A5260s

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Background. The adipokines leptin and adiponectin, produced primarily by adipose tissue, have diverse endocrine and immunologic effects, and circulating levels reflect adipocyte lipid content, local inflammation, and tissue composition. We assessed relationships between changes in regional fat depots, leptin and adiponectin levels, and metabolic and inflammatory markers over 96 weeks in the AIDS Clinical Trials Group (ACTG) A5260s metabolic substudy of the A5257 randomized trial of tenofovir disoproxil fumarate/emtricitabine plus atazanavir/ritonavir, darunavir/ritonavir, or raltegravir among treatment-naive persons with human immunodeficiency virus (PWH).

Methods. Fat depots were measured using dual-energy absorptiometry and abdominal computed tomographic imaging at treatment initiation and 96 weeks later. Serum leptin and adiponectin, homeostatic model assessment of insulin resistance (HOMA-IR), and high-sensitivity C-reactive protein (hsCRP) were measured at the same timepoints. Multivariable regression models assessed relationships between fat depots, adipokines, HOMA-IR, and hsCRP at week 96.

Results. Two hundred thirty-four participants maintained viral suppression through 96 weeks (90% male, 29% black, median age 36 years). Serum leptin increased over 96 weeks (mean change 22%) while adiponectin did not (mean change 1%), which did not differ by study arm. Greater trunk, limb, and abdominal subcutaneous and visceral fat were associated with higher HOMA-IR and hsCRP at 96 weeks, but serum leptin level was a stronger determinant of these endpoints using a mediation model approach. A similar mediating effect was not observed for adiponectin.

Conclusions. Higher circulating leptin is associated with greater HOMA-IR and hsCRP independent of fat depot size, suggesting that greater adipocyte lipid content may contribute to impaired glucose tolerance and systemic inflammation among PWH starting antiretroviral therapy.

Keywords. HIV; adipose tissue; adipokines; metabolism; leptin.

Weight gain following antiretroviral therapy (ART) initiation is common among persons with human immunodeficiency virus (PWH) [1] and frequently characterized by greater adipose tissue accumulation relative to lean mass [2, 3]. Adipose tissue produces numerous signaling molecules with local and distal effects on energy intake, storage, and metabolism, including targets in the central nervous system (CNS), heart and blood vessels, liver, skeletal muscle, gastrointestinal tract, and innate and adaptive immune systems, among others [4, 5]. Circulating levels of adipokines are affected by changes in overall adiposity, the anatomic distribution of fat depots, adipocyte size and lipid content, and the composition of adipose tissue immune cells [6, 7].

Leptin and adiponectin are 2 principal circulating adipokines regulating metabolism and immune function. White adipose tissue is the primary site of leptin production [5], and leptin expression and circulating levels are higher if the adipose tissue expands by adipocyte hypertrophy (increased lipid storage per cell) vs adipocyte hyperplasia (increased number of cells) [8, 9]. Leptin has a dual role as a hormone modulating energy homeostasis, reproductive function, bone metabolism, and other systems, and as a cytokine modulating innate and adaptive immune function [4–6, 10]. A primary function of leptin is to regulate body weight and counteract metabolic dysfunction during periods of overnutrition by increasing lipolysis and glucose uptake, inhibiting hepatic glucose output, and suppressing appetite [11, 12].

Circulating adiponectin levels typically fall with increasing adiposity, though reduced expression is more driven by increased adipose tissue inflammation rather than increased

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adipocyte size or lipid content [8, 13]. Adiponectin targets diverse tissues, including the liver, skeletal muscle, the vasculature, and immune cells, and has insulin-sensitizing, antiatherogenic, and anti-inflammatory properties [14, 15]. Among obese individuals, lower adiponectin levels are a key feature differentiating the metabolically unhealthy from the metabolically healthier [16, 17].

Prior studies demonstrated altered adipokine levels in PWH with clinically overt lipodystrophy syndromes [18], but there are few data on changes in leptin and adiponectin levels in relation to weight gain on ART, body composition, and metabolic and inflammatory biomarkers among individuals on newer regimens, including integrase strand transfer inhibitors (INSTIs). The AIDS Clinical Trials Group (ACTG) A5260s study randomized treatment-naive PWH to initiate tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) plus atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL) [19]. Prior analyses from this cohort found a disproportionate accumulation of adipose tissue in the visceral as compared to subcutaneous limb or abdominal compartments over 96 weeks [2], and weight gain on ART was associated with increased insulin resistance and higher serum inflammatory markers [20, 21]. Here, we investigated how qualitative changes in adipose tissue, as reflected in circulating adipokine levels, may affect metabolic health and systemic inflammation by assessing relationships between adiposity, serum adiponectin and leptin levels, and A5260s endpoints over 96 weeks. To this end, we used a mediation model approach (Figure 1) to assess whether serum leptin and adiponectin levels are more closely associated with insulin resistance and inflammation compared to radiographic measurements of regional adiposity.

METHODS

Study Population

The A5260s substudy of the ACTG A5257 phase 3 randomized, open-label clinical trial enrolled 334 participants with no known cardiovascular disease or diabetes, uncontrolled thyroid disease, or use of lipid-lowering medications from 26 sites in the United States from June 2009 to April 2011 as previously reported [19]. A primary objective of A5260s was to compare cardiovascular markers [22], and secondary objectives included assessing changes in inflammation and immune activation markers [20], insulin resistance [21], and body composition between those initiating the randomized regimens (TDF/FTC plus ATV/r, DRV/r, or RAL) [2]. Two hundred thirty-four participants with a human immunodeficiency virus type 1 (HIV-1) RNA <50 copies/mL at 24 weeks, viral suppression sustained through 96 weeks, and no reported ART interruptions of more than 7 days were classified as successfully treated. Serum biomarkers were measured as previously described [19–22]. The parent A5257 study and the A5260s substudy were approved by the institutional review boards at participating institutions, and participants provided written informed consent.

Body Composition Measures

Radiographic assessments of body composition were performed at baseline and week 96. Whole-body dual-energy absorptiometry (DXA) was used to quantify total limb fat (the sum of upper and lower extremity fat) and trunk fat. A single-slice computed tomography (CT) scan at the L4–L5 level was used to quantify abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Imaging was standardized and centrally read by blinded personnel at the Body Composition Analysis Center at Tufts University (Boston, Massachusetts; DXA) and LA Biomed (Torrance, California; CT).

Statistical Analyses

Demographic information, including race/ethnicity, age, and sex, was collected at entry, along with smoking status, body mass index (BMI; kg/m^2), CD4$^+$ cell count (cells/mm^3), and HIV-1 RNA level (copies/mL). Baseline characteristics of the cohort, stratified by regimen, were calculated as medians with interquartile ranges for continuous variables and percentages for categorical variables. We assessed the fold-change in leptin and adiponectin levels at 48 and 96 weeks compared to baseline for each of the 3 regimens, and compared the ATV/r and DRV/r arms to the RAL arm at each time point. The

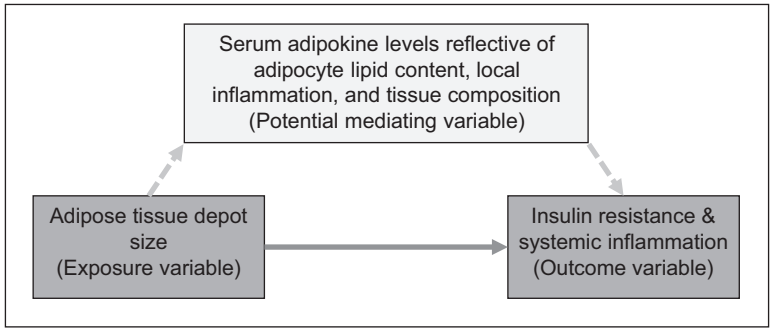

Figure 1. Mediation model design.

relationships between the change from baseline in leptin and adiponectin levels with the change in fasting glucose, homeostatic model assessment of insulin resistance (HOMA-IR), D-dimer, and immunologic markers were assessed using Spearman correlations at 48 and 96 weeks, and the results displayed as a heatmap. We assessed the fold-change in leptin and adiponectin levels for every 10% increase in regional fat depots, or 1% increase in BMI, from baseline to week 96 using linear regression models adjusted for age, sex, race, baseline BMI (omitted from the model with BMI as the exposure variable) and pretreatment $CD4^+$ T-cell count and HIV-1 RNA.

To assess whether serum adipokine levels may better estimate the effects of adiposity on metabolic health and inflammation compared to radiographic measurements, we employed a statistical mediation framework with 3 sequential sets of multivariable linear regression models incorporating 96-week body composition parameters, leptin and adiponectin, HOMA-IR, and high-sensitivity C-reactive protein (hsCRP). This approach was selected based on our hypothesis that adipocyte lipid content and adipose tissue inflammation, reflected in serum adipokine levels, are a principal driver of metabolic dysregulation and systemic inflammation (Figure 1). First, the association between the exposure (body composition) and the outcome variable (HOMA-IR or hsCRP) was assessed. Second, the association between the exposure variable (body composition) and the potential mediator (leptin or adiponectin) was examined. Third, we evaluated whether there was attenuation in the effect of exposure (body composition) on the outcome (HOMA-IR or hsCRP) after adjustment for the potential mediator (leptin or adiponectin) [23]. All regression models were adjusted for age, sex, race, BMI, and pretreatment $CD4^+$ T-cell count and HIV-1 RNA. Analysis was performed using SAS version 9.4 software.

RESULTS

Cohort Characteristics

The analysis included 234 participants classified as successfully treated; 90% were male, 29% were black non-Hispanic, and 19% were Hispanic (Table 1). At entry the median age was 36 years, CD4 was 338 cells/μL, BMI was 25 kg/m^2, and serum adiponectin was 3.90 $\log_{10}$ ng/mL and leptin was 3.61 $\log_{10}$ pg/mL. As previously reported, participants in A5260s had significant increases in limb fat (13%), trunk fat (18%), and abdominal SAT (20%) and VAT (26%) over 96 weeks, which did not differ by study arm [2].

Changes in Leptin and Adiponectin Over 96 Weeks

Serum leptin levels increased in all arms at 48 and 96 weeks from baseline (Supplementary Table). The 48-week increase was larger in the ATV/r (25%) and RAL (26%) arms compared to DRV/r (12%), but 96-week increases were similar between arms (21%, 27%, and 29% for ATV/r, DRV/r, and RAL, respectively). The change in leptin at 48 and 96 weeks for ATV/r and DRV/r was not significantly different compared to RAL.

The change in serum adiponectin was less pronounced than for leptin and characterized by an initial rise at 48 weeks that attenuated at 96 weeks. Adiponectin increased by 9%, 8% and

Table 1. Cohort Baseline Characteristics by Treatment Arm (N = 234)

Characteristic	Atazanavir/Ritonavir (n = 68)	Raltegravir (n = 82)	Darunavir/Ritonavir (n = 84)
Age	38 (31–44)	36 (27–45)	36 (28–47)
Male sex, %	93	89	88
Race/ethnicity, %			
White	51	44	49
Black	31	28	29
Hispanic	16	20	21
Current smoking, %	32	34	32
$CD4^+$ count, cells/μL	294 (180–461)	347 (246–450)	337 (172–424)
HIV-1 RNA, $\log_{10}$ copies/mL	4.76 (4.03–5.15)	4.48 (3.96–4.94)	4.62 (3.98–4.95)
Weight, kg	82 (71–90)	78 (68–89)	77 (65–84)
BMI, kg/m^2	26 (23–29)	25 (22–28)	24 (22–27)
Limb fat, kg	8.6 (6.4–11.2)	7.3 (5.2–11.5)	7.9 (5.1–10.0)
Trunk fat, kg	9.6 (6.8–12.9)	9.9 (6.1–13.3)	9.0 (5.9–11.9)
SAT, cm^2	222.2 (138.0–308.3)	213.2 (128.3–291.5)	181.3 (117.4–266.4)
VAT, cm^2	76.4 (41.2–109.2)	78.0 (41.6–111.9)	67.0 (38.6–104.8)
Lean body mass, kg	59.1 (51.4–64.3)	54.8 (49.3–61.0)	55.1 (46.7–59.9)
Leptin, $\log_{10}$ pg/mL	3.71 (3.33–3.95)	3.61 (3.20–3.91)	3.53 (3.16–3.87)
Adiponectin, $\log_{10}$ ng/mL	3.87 (3.74–4.01)	3.91 (3.74–4.11)	3.91 (3.77–4.06)

Data are presented as median (IQR) unless otherwise indicated.

Abbreviations: BMI, body mass index; HIV-1, human immunodeficiency virus; IQR, interquartile range; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

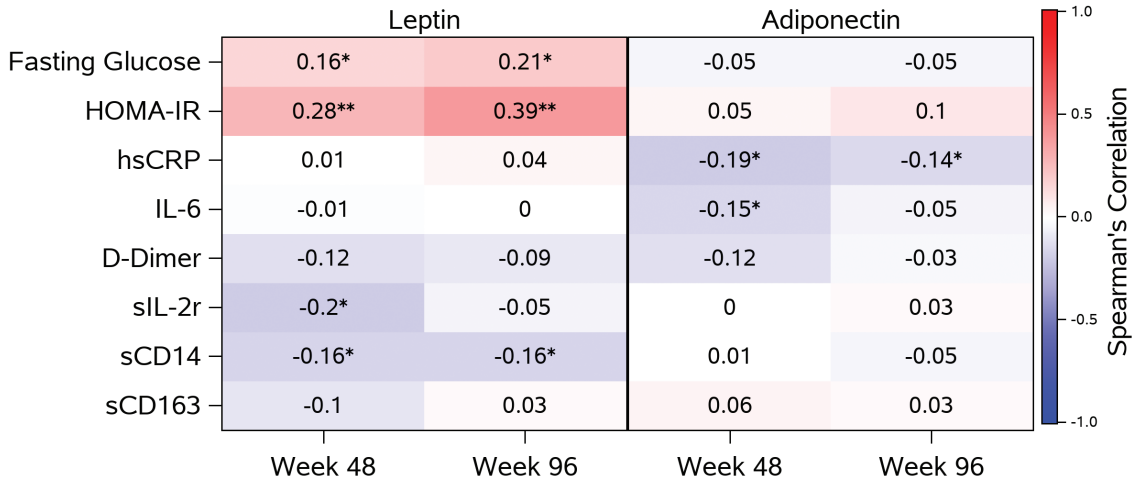

Figure 2. Spearman correlations for concurrent change in leptin or adiponectin with metabolic and inflammation biomarkers from baseline to 48 and 96 weeks. Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; sCD14, soluble CD14; sCD163, soluble CD163; sIL-2r, soluble interleukin 2 receptor. *$P < .05$; **$P < .0001$.

1% in the ATV/r, DRV/r, and RAL arms, respectively, at 48 weeks, but differed from baseline by 5%, 1%, and −2% at 96 weeks. The increase in adiponectin levels was significantly greater in the ATV/r arm at 96 weeks compared to the RAL arm ($P = .02$).

Changes in Adipokines and Metabolic and Inflammatory Markers Over 96 Weeks

As shown in the heatmap (Figure 2), an increase in leptin from baseline to 48 weeks was correlated with an increase in fasting glucose ($r = 0.16$) and HOMA-IR ($r = 0.28$) over the same period, and with a decrease in soluble interleukin 2 (IL-2) receptor ($r = –0.20$) and soluble CD14 (sCD14; $r = –0.16$) ($P < .05$ for all). Similar results were seen for the correlation of the change in leptin with changes in fasting glucose, HOMA-IR, and sCD14 at 96 weeks ($P < .05$ for all).

In contrast, the change in adiponectin was not associated with the change in glucose or HOMA-IR at 48 or 96 weeks, but a decline in adiponectin from baseline to 48 weeks was associated with a rise in hsCRP ($r = –0.19$) and interleukin 6 (IL-6; $r = –0.15$) over the same period ($P < .05$ for both). However, by 96 weeks only the inverse correlation between the change in adiponectin and the change in hsCRP remained significant ($r = –0.14$).

Changes in Body Composition and Adipokines Over 96 Weeks

We assessed relationships between changes in body composition parameters with the change in leptin and adiponectin from baseline to 96 weeks (Table 2). A 10% increase in limb fat was associated with a 1.14-fold increase in leptin over 96 weeks, which was similar to that of trunk fat (1.13-fold) but greater than that for SAT (1.08-fold) and VAT (1.03-fold). Conversely, a 10% gain in limb fat was associated with a 0.94-fold reduction in adiponectin, as compared to 0.95-fold for trunk fat, 0.97-fold for SAT, and 0.98-fold for VAT. Last, each 1% gain in BMI was associated with a 1.05-fold increase in leptin and a 0.98-fold reduction in adiponectin.

Relationships of Adipokines, Body Composition, and HOMA-IR and hsCRP at 96 Weeks

Given the correlation between changes in leptin and HOMA-IR, and the inverse correlation between adiponectin and hsCRP,

Table 2. Fold-Change in Leptin and Adiponectin for Every 10% Increase in Body Composition Parameter From Baseline to Week 96

	Leptin			Adiponectin		
Parameter	Adjusted[a] Fold Change at 96 Weeks	(95% CI)	*P* Value	Adjusted[a] Fold Change at 96 Weeks	(95% CI)	*P* Value
Trunk fat	1.13	(1.11–1.15)	<.001	0.95	(.93–.96)	<.001
Limb fat	1.14	(1.11–1.16)	<.001	0.94	(.92–.96)	<.001
SAT	1.08	(1.06–1.09)	<.001	0.97	(.96–.99)	<.001
VAT	1.03	(1.02–1.04)	<.001	0.98	(.98–.99)	<.001
BMI[b]	1.05	(1.05–1.06)	<.001	0.98	(.97–.98)	<.001

Abbreviations: BMI, body mass index; CI, confidence interval; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

[a]Adjusted for sex, race/ethnicity, and baseline age, viral load, CD4 count, and BMI.

[b]Fold-change per 1% increase in BMI; BMI model does not adjust for BMI as a covariate.

observed over 96 weeks (Table 2), we assessed whether serum adipokine levels may better estimate the effects of adiposity on metabolic health and inflammation compared to radiographic measurements using a mediation model approach (Figure 1).

At 96 weeks, higher trunk fat, limb fat, SAT, and VAT were associated with higher HOMA-IR and hsCRP (Table 3) after adjusting for age, sex, race, BMI, and pretreatment $CD4^+$ T-cell count and HIV-1 RNA. Higher trunk fat, limb fat, SAT, and VAT were also associated with higher leptin at 96 weeks. The addition of leptin to the body composition and HOMA-IR models abrogated the statistical significance of relationships between trunk fat, limb fat, SAT, and VAT with HOMA-IR. For example, the point estimate for the effect of trunk fat on HOMA-IR changed from 0.35 ($P < .001$) to 0.01 ($P = .92$) after the addition of leptin to the model, with similar changes observed for other body composition parameters. A potential mediating role for leptin on the association of adiposity and hsCRP was only observed for limb fat and SAT.

Greater limb fat, trunk fat, SAT, and VAT were associated with lower serum adiponectin. However, the addition of adiponectin to the body composition and HOMA-IR models, and the body composition and hsCRP models, did not suggest any mediating effect of the adipokine (data not shown). Last, all mediation models were further adjusted for treatment arm (ATV/r, DRV/r, or RAL) and results were similar to the primary analysis (data not shown).

DISCUSSION

In light of recent studies showing greater weight gain among PWH initiating INSTI-based ART [24], and the rising prevalence of overweight and obesity [1], there is a critical need to understand the consequences of excess adiposity in the HIV population. The principal findings from this analysis of the A5260s substudy of ACTG clinical trial A5257 are that treatment-naive adults have an increase in leptin, and a proportionally smaller decrease in adiponectin, with body fat gains over 96 weeks of ART, which does not differ between INSTI and protease inhibitor–based regimens. Second, the greatest relative changes in leptin and adiponectin occurred with increases in trunk fat and limb fat, whereas the smallest changes occurred with increases in VAT. Third, an increase in circulating leptin was associated with a concomitant rise in insulin resistance over 96 weeks, while a decrease in adiponectin was associated with a rise in hsCRP over the same period. Last, leptin levels appeared to mediate associations between trunk fat, limb fat, SAT, and VAT with HOMA-IR at 96 weeks of ART, and between limb fat and SAT with hsCRP, which was not observed for adiponectin. This finding suggests that adipocyte size and lipid content, reflected in circulating leptin levels, are major contributors to the metabolic and inflammatory status of PWH on ART independent of fat mass.

We observed that the greatest relative changes in leptin and adiponectin occurred with increases in trunk fat and limb fat, whereas the smallest changes occurred with increases in VAT, which was unexpected. We suggest 3 potential mechanisms for this finding: first, that VAT adipokines may be partially cleared by the liver before reaching circulation; second, that higher leptin secretion from subcutaneous compared to visceral fat, as shown in prior studies, is reflected in a greater proportional change with weight gain in the trunk and limbs [25, 26]; or third, that a difference in the relative balance of adipocyte hypertrophy vs hyperplasia in visceral and subcutaneous depots leads to differential effects on serum adipokine levels. Additional studies are warranted to explore this further.

Several factors may alter adipocyte biology in PWH. HIV viral proteins and some ART medications impair adipogenesis, principally by promoting adipocyte hypertrophy over hyperplasia through reduced expression of peroxisome proliferator-activated receptor–γ and other key regulatory proteins [27, 28], while interference with mitochondrial function can also alter adipokine synthesis [29]. Furthermore, a recent study found increased adipocyte size and adipogenic marker expression in SAT and VAT from noninfected macaques treated with RAL or dolutegravir compared to controls, whereas in vitro treatment of adipocytes with dolutegravir and, to a lesser extent, RAL was associated with greater lipid accumulation [30]. Hypertrophied adipocytes are more prone to hypoxia and apoptosis, which promotes recruitment of macrophages and other immune cells, inflammation, fibrosis, and impaired insulin signaling [31, 32]. Indeed, a prior analysis of the A5260s study found that lower SAT and VAT density, which can reflect the accumulation of less radiologically dense lipid, was correlated with higher IL-6, HOMA-IR, and leptin levels after 96 weeks of ART [33]. Going forward, studies to assess the consequences of weight gain on ART should consider the composition, not simply the quantity, of adipose tissue.

We observed a positive correlation between the change in leptin and HOMA-IR at both 48 and 96 weeks, but no association between the change in adiponectin and HOMA-IR at either timepoint. Leptin inhibits hunger and stimulates satiety via the CNS, promotes adipocyte lipolysis, increases peripheral glucose uptake, and inhibits hepatic glucose output [11, 12]. Together, these effects maintain metabolic homeostasis and prevent weight gain. This regulatory mechanism is hindered by behaviors leading to excessive caloric intake and/or insufficient energy expenditure, medications promoting weight gain, a "leptin resistance" phenotype in some individuals, and other factors contributing to excessive adiposity [34]. In these individuals, leptin secretion from adipocytes remains chronically elevated in the setting of worsening metabolic function, which promotes release of lipids into circulation, blunts pancreatic insulin output, and can accelerate a transition from insulin resistance to overt type 2 diabetes [35]

Table 3. Effect of Leptin on the Relationship of Week 96 Body Composition With Homeostatic Model Assessment of Insulin Resistance and High-Sensitivity C-Reactive Protein (Mediation Model Approach)

	Effect of Leptin on the Relationship of Week 96 Body Composition With HOMA-IR (Mediation Model Approach)					
	Model 1		Model 2		Model 3	
	Exposure: Body Composition Outcome: HOMA-IR		Exposure: Body Composition Outcome: Leptin		Exposure: Body Composition Potential Mediator: Leptin Outcome: HOMA-IR	
Week 96 Body Composition Parameter	Adjusted Week 96 HOMA-IR (95% CI)	*P* Value	Adjusted Week 96 Leptin (95% CI)	*P* Value	Adjusted Week 96 HOMA-IR (95% CI)	*P* Value
Trunk fat (kg)	**0.35 (.24–.46)**	**<.001**	**0.67 (.59–.76)**	**<.001**	**0.01 (–.15 to .17)**	**.92**
Limb fat (kg)	**0.30 (.16–.44)**	**<.001**	**0.70 (.59–.81)**	**<.001**	**–0.12 (–.29 to .05)**	**.16**
SAT (cm^2)	**0.01 (.009–.014)**	**<.001**	**0.02 (.02–.02)**	**<.001**	**–0.001 (–.006 to .004)**	**.73**
VAT (cm^2)	**0.017 (.009–.026)**	**<.001**	**0.03 (.03–.04)**	**<.001**	**0.000 (–.009 to .009)**	**.95**
	Effect of Leptin on the Relationship of Week 96 Body Composition With hsCRP (Mediation Model Approach)					
	Model 1		Model 2		Model 3	
	Exposure: Body Composition Outcome: hsCRP		Exposure: Body Composition Outcome: Leptin		Exposure: Body Composition Potential Mediator: Leptin Outcome: hsCRP	
	Adjusted Week 96 hsCRP (95% CI)	*P* Value	Adjusted Week 96 Leptin (95% CI)	*P* Value	Adjusted Week 96 hsCRP (95% CI)	*P* Value
Trunk fat (kg)	0.36 (.19–.54)	<.001	0.67 (.59–.76)	<.001	0.25 (–.00 to .51)	.05
Limb fat (kg)	**0.26 (.05–.47)**	**.02**	**0.70 (.59–.81)**	**<.001**	**0.01 (–.27 to .28)**	**.97**
SAT (cm^2)	**0.01 (.003–.016)**	**.002**	**0.02 (.02–.02)**	**<.001**	**0.004 (–.004 to .012)**	**.34**
VAT (cm^2)	0.024 (.012–.037)	<.001	0.03 (.03–.04)	<.001	0.017 (.003–.031)	.02

Rows shown in bold fulfill criteria for leptin mediation of the relationship between the body composition parameter and HOMA-IR or hsCRP.

Model 1: Week 96 level (log_{10}) of HOMA-IR or hsCRP for every 10 units higher in body composition parameter, adjusted for age, sex, race, BMI, and pretreatment $CD4^+$ T-cell count and HIV-1 RNA.

Model 2: Week 96 level (log_{10}) of leptin for every 10 units higher in body composition adjusted for age, sex, race, BMI, and pretreatment $CD4^+$ T-cell count and human immunodeficiency virus type 1 RNA.

Model 3: Model 1 further adjusted for week 96 leptin.

Abbreviations: CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

The accumulation of adipose tissue is accompanied by increased systemic inflammation. We observed a potential mediating role for leptin on the relationship of limb fat and SAT with hsCRP, which has previously been reported for BMI and hsCRP in a smaller cohort [36]. The structure of leptin is similar to the long-chain helical cytokine family (eg, IL-2 and IL-6) [37], and leptin receptors are expressed on cells of the innate and adaptive immune system [38, 39]. Leptin promotes monocyte and macrophage activation, proliferation, and proinflammatory cytokine expression, and promotes T-cell proliferation, Th1 phenotype polarization, and interferon-γ production [38, 39].

While adiponectin is considered an anti-inflammatory and "insulin sensitizing" adipokine, it did not appear to mediate relationships between fat depot size and HOMA-IR or hsCRP at 96 weeks in the same manner as leptin. However, we did observe an inverse association between the changes in adiponectin and hsCRP at 48 and 96 weeks. While adiponectin inhibits local macrophage differentiation and production of tumor necrosis factor–α and other cytokines [40], a progressive increase in adipose tissue inflammation is accompanied by reduced adiponectin expression [13]. This complex interaction of inflammation and adiponectin production within adipose tissue may not be clearly reflected in circulating biomarker levels.

Our analysis had limitations, including lack of data on weight change and adipokine levels from the time of HIV seroconversion to the start of ART, which precluded an assessment of whether participants were returning to a prior, healthy physiologic state vs gaining weight beyond their prior baseline. RAL was the first INSTI-class medication approved for the treatment of HIV and our results may not be representative of persons receiving dolutegravir or bictegravir, 2 agents associated with greater weight gain among ART-naive individuals [24]. The study cohort was predominantly male, and due to sex differences in adipokine levels the results may not be generalizable to females. Our finding that changes in leptin and adiponectin were greater for increases in trunk and limb fat compared to VAT was unexpected and warrants further exploration. Finally, the study duration of 96 weeks was insufficient to assess incident metabolic and cardiovascular disease diagnoses or events, which will require more long-term follow-up.

In summary, treatment-naive PWH starting modern INSTI and protease inhibitor–based ART regimens had a similar increase in leptin, and a relatively smaller decrease in adiponectin, with weight gain over 96 weeks. Leptin did not appear to be simply a marker of increased adiposity, but rather mediated the relationship of adiposity with insulin resistance and inflammation. Further studies to assess the determinants of adipokine expression and the health of adipocytes may illuminate novel avenues to predict and mitigate the development of cardiometabolic diseases in PWH.

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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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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