HIV and Obesity Comorbidity Increase Interleukin 6 but Not Soluble CD14 or D-Dimer

Barbara S. Taylor, MD, MS, Kaku So-Armah, PhD,† Janet P. Tate, ScD,‡ Vincent C. Marconi, MD,§ John R. Koethe, MD,‖ Roger J. Bedimo, MD,¶ Adeel A. Butt, MD, MS,# Cynthia L. Gibert, MD,** Matthew B. Goetz, MD,†† Maria C. Rodriguez-Barradas, MD,‡‡ Julie A. Womack, CNM, APRN, PhD,§§ Mariana Gerschenson, PhD,‖‖ Vincent Lo Re, III, MD, MSCE,¶¶ David Rimland, MD,§ Michael T. Yin, MD, MS,## David Leaf, MD,*** Russell P. Tracy, PhD,††† Amy C. Justice, MD, PhD,‡ and Matthew S. Freiberg, MD‡‡‡*

Objectives: Obesity prevalence among people living with HIV (HIV+) is rising. HIV and obesity are proinflammatory states, but their combined effect on inflammation (measured by interleukin 6, IL-6), altered coagulation (D-dimer), and monocyte activation (soluble CD14, sCD14) is unknown. We hypothesized inflammation increases when obesity and HIV infection co-occur.

Methods: The Veterans Aging Cohort Study survey cohort is a prospective, observational study of predominantly male HIV+ veterans and veterans uninfected with HIV; a subset provided blood samples. Inclusion criteria for this analysis were body mass index $\geq$ 18.5 kg/m^2 and biomarker measurement. Dependent variables were IL-6, sCD14, and D-dimer quartiles. Obesity/HIV status was the primary predictor. Unadjusted and adjusted logistic regression models were constructed.

Results: Data were analyzed for 1477 HIV+ and 823 uninfected participants. Unadjusted median IL-6 levels were significantly higher and sCD14 levels significantly lower in obese/HIV+ compared with nonobese/uninfected (P <0.01 for both). In adjusted analyses, the odds ratio for increased IL-6 in obese/HIV+ patients was 1.76 (95% confidence interval: 1.18 to 2.47) compared with nonobese/uninfected, and obesity/HIV+ remained associated with lower odds of elevated sCD14. We did not detect a synergistic association of co-occurring HIV and obesity on IL-6 or sCD14 elevation. D-dimer levels did not differ significantly between body mass index/HIV status groups.

Conclusions: HIV–obesity comorbidity is associated with elevated IL-6, decreases in sCD14, and no significant difference in D-dimer. These findings are clinically significant, as previous studies associated these biomarkers with mortality. Future studies should assess

Received for publication December 9, 2016; accepted March 30, 2017.

From the *Medical Service/Infectious Diseases, South Texas Veterans Health Care System, San Antonio, TX; Department of Medicine, UT Health San Antonio, San Antonio, TX; †Department of Medicine, Boston University School of Medicine, Boston, MA; ‡Section of General Internal Medicine, VA Connecticut Healthcare System, West Haven, CT; Department of Internal Medicine, Yale University School of Medicine, New Haven, CT; §Medical Service, VA Medical Center, Atlanta, GA; Medical Service, Emory University School of Medicine, Atlanta, GA; ||Departments of Medicine and Biostatistics, Vanderbilt University School of Medicine, Nashville, TN; ¶Department of Medicine, Infectious Diseases Section, VA North Texas Health Care System; UT Southwestern Medical Center, Dallas, TX; #Center for Health Equity Research and Promotion, VA Pittsburg Healthcare System, Pittsburgh, PA; Hamad Healthcare Quality Institute, Hamad Medical Corporation, Doha, Qatar; Department of Medicine, Weill Cornell Medical College, Doha, Qatar and New York, NY; **Medical Service/Infectious Diseases, VA Medical Center, Washington, DC; Department of Medicine, George Washington University Medical Center, Washington, DC; ††Department of Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA; David Geffen School of Medicine at UCLA, Los Angeles, CA; ‡‡Infectious Diseases Section, Michael E. DeBakey VA Medical Center, Houston, TX; Infectious Diseases Section, Baylor College of Medicine, Houston, TX; §§VA Connecticut Healthcare System, West Haven, CT; ‖‖Cell and Molecular Biology Department, John A. Burns School of Medicine, University of Hawaii- Manoa, Honolulu, HI; ¶¶Philadelphia VA Medical Center, Philadelphia, PA; Perelman School of Medicine, University of Pennsylvania, Philadelphia, VA; ##Division of Infectious Diseases, Columbia University Medical Center, New York, NY; ***Infectious Diseases Section, VA Greater Los Angeles Healthcare System, Los Angeles, CA; Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA; †††Departments of Pathology and Laboratory Medicine and Biochemistry, College of Medicine, University of Vermont, Burlington, VT; and ‡‡‡Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN; Geriatric Research, Education, and Clinical Center, VA Tennessee Valley Healthcare System, Nashville, TN.

Supported by National Institute of Allergy and Infectious Diseases at the National Institutes of Health K23AI081538 (B.S.T.), American Heart Association, National Center Mentored Clinical and Population Research Award 14CRP20150023 (B.S.T.), National Institute on Alcohol Abuse and Alcoholism and National Heart Lung and Blood Institute at the National Institutes of Health R01HC095136-04 and 5R01HC095126-04 (M.S.F.), and National Institute on Alcohol Abuse and Alcoholism U10 AA 13566 (Veterans Aging Cohort Study).

Presented at *2016 Conference on Retroviruses and Opportunistic Infections.* Poster Presentation; February 22–25, 2016; Boston, MA. B.S.T., K.S.-A., J.P.T., V.C.M., R.B., A.A.B., C.L.G, M.G., M.C.R.-B, M.S.F. "HIV & Obesity Synergistically Increase Interleukin 6 but not Soluble CD14 or D-dimer."

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Barbara S. Taylor, MD, MS, Department of Medicine, Division of Infectious Diseases, University of Texas Health Science Center San Antonio, 7703 Floyd Curl Dr. MSC-7881 San Antonio, TX 78229-3900 (e-mail: TaylorB4@uthscsa.edu).

whether other biomarkers show similar trends and potential mechanisms for unanticipated sCD14 and D-dimer findings.

Key Words: HIV, obesity, inflammation, monocyte activation, coagulation, VACS

(*J Acquir Immune Defic Syndr* 2017;75:500–508)

INTRODUCTION

Obesity is a leading health threat in the United States[1–3] and is more common in minorities and those with lower socioeconomic status.[4–9] These same individuals are also most severely impacted by the HIV epidemic.[10,11] Because potent antiretroviral therapy (ART) is now widely available, weight loss previously associated with untreated HIV infection has been supplanted by weight gain. Consequently, obesity is increasingly common in people living with HIV infection.[12–17]

Both obesity and HIV infection independently increase risk for cardiovascular disease (CVD).[18–22] A hypothesized mechanism for the increased cardiovascular risk, common to both, is immune system alteration.[23–29] Although obesity has well-established associations with traditional risk factors for CVD including hypertension, hyperlipidemia, and diabetes, both HIV and obesity are associated with immune system alterations that may independently impact risk.[23–28] Although both HIV and obesity are associated with altered immunity, their combined effect on inflammation, altered coagulation, and monocyte activation is unclear.

We hypothesized that the combination of obesity and HIV infection (obesity/HIV) is associated with increased inflammation when compared with either condition alone or the absence of both conditions. In a subset of participants from the Veterans Aging Cohort Study (VACS) survey cohort, we examined the relationship between obesity/HIV and biomarkers of inflammation (interleukin 6), altered coagulation (D-dimer), and monocyte activation (soluble CD14, sCD14). These 3 biomarkers were chosen because they represent different inflammatory pathways and are altered in the context of HIV and obesity.[23,30–33]

METHODS

Study Design and Setting

This is a cross-sectional analysis of data from the VACS. The VACS survey cohort is a prospectively enrolled observational longitudinal study of veterans living with HIV (HIV+) and veterans who are uninfected with HIV (uninfected) matched (1:1) on age, sex, race/ethnicity, and geographic location.[34] In 2005–2007, a subset of this cohort (1525 HIV+ and 843 uninfected) participants consented to provide blood samples as previously described.[27] Those with body mass index (BMI) $\geq$18.5 kg/m^2 (ie, not underweight) and with available measurements of IL-6, sCD14, or D-dimer were eligible for inclusion in the present analyses.

Dependent and Independent Variables

IL-6, sCD14, and D-dimer were the dependent variables. They were analyzed as continuous variables for descriptive analyses and categorized into quartiles for regression analyses, as the relationships between BMI and all 3 biomarkers were nonlinear (Supplemental Digital Content Figure, http://links.lww.com/QAI/B28). IL-6 and D-dimer were log transformed to better approximate the normal distribution. Specimens used to measure these biomarkers were collected using serum separator and EDTA blood collection tubes and shipped to a central repository at the Massachusetts Veterans Epidemiology Research and Information Center in Boston, MA. Measurements of these biomarkers are further described in previous work.[27]

To construct the independent variable, we classified obesity (BMI) $\geq$ 30 kg/m^2 by HIV status to create 4 mutually exclusive categories. We chose obesity as a threshold because overweight status (BMI $\geq$ 25 kg/m^2 and $<$30 kg/m^2) may not be associated with adverse outcomes in the general population or among people living with HIV.[3,15,18] Underweight (BMI $<$18.5 kg/m^2) was excluded because of the small number in the cohort (n = 48). People with BMI 18.5–30 kg/m^2 who were HIV uninfected (nonobese/HIV) were defined as the referent group.

Covariates

Covariates were assessed closest to the time of blood specimen collection for IL-6, sCD14, and D-dimer measurements. Sociodemographic data included age, sex, and race/ethnicity. CVD was defined using previously validated diagnostic or procedural codes for myocardial infarction, unstable angina, congestive heart failure, coronary revascularization, or ischemic stroke.[35,36] Hypertension was defined as receipt of antihypertensive therapy prescription or blood pressure $\geq$140/90 mm Hg based on the average of the last 3 outpatient measurements, as previously described.[21,37,38] Diabetes was defined using a validated algorithm that includes glucose measurements, use of insulin or oral hypoglycemic agents, and/or *International Classification of Diseases, Ninth Revision (ICD-9)* codes.[39] Smoking was self-reported using a standardized survey.[40] Total cholesterol measurements were dichotomized at 200 mg/dL, low-density lipoprotein cholesterol at 160 mg/dL, high-density lipoprotein (HDL) cholesterol at 40 mg/dL, and triglycerides at 200 mg/dL.[21,41] HMG CoA reductase inhibitor (statin) prescriptions were assessed using data from the VA Corporate Data Warehouse.

Using the Alcohol Use Disorders Identification Test (AUDIT-C) and alcohol abuse/dependence *ICD-9* codes, we categorized alcohol use as follows: (1) no current drinking, (2) low-risk current drinking (AUDIT-C $<$4), (3) at risk or heavy drinking (AUDIT-C$\geq$4), and (4) alcohol abuse or dependence diagnosis.[42] History of cocaine use was defined by self-report. Hepatitis C virus (HCV) infection status was based on a positive HCV antibody test or at least 1 inpatient and/or 2 outpatient *ICD-9* codes.[43] Advanced liver fibrosis was estimated as a Fibrosis-4 index score $>$3.25 using participant age, platelet count, aspartate aminotransferase, and alanine aminotransferase levels.[44,45] Anemia was defined as hemoglobin $<$12g/dL. Chronic kidney disease (stage 3–5) was defined as an estimated glomerular filtration rate of $<$60

$mL \cdot min^{-1} \cdot 1.73\ m^{-2}$.[46] Any history of cancer up to time of biomarker assessment was determined using VA Central Cancer Registry data.[47] For HIV-infected participants, we also assessed HIV-1 RNA level, dichotomized at 500 copies/mL as in previous VACS studies,[21,38] $CD4^+$ T-cell (CD4) count dichotomized at 500 cells/mm^3, and ART regimen: nucleoside/nucleotide reverse transcriptase inhibitors plus protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitor plus nonnucleoside reverse transcriptase inhibitors, other, or no ART.[21]

Statistical Analysis

We compared continuous variables (Kruskall–Wallis rank test) and categorical variables (χ^2 test) by BMI categories overall and stratified by HIV status. We assessed correlations of obesity/HIV status with IL-6, sCD14, and D-dimer. We then constructed logistic regression models to estimate the association between obesity/HIV comorbidity and elevated (highest quartile vs lower 3 quartiles) IL-6, sCD14, or D-dimer. Logistic regression analyses were first adjusted for age and race/ethnicity and subsequently adjusted for diabetes, CVD, HCV infection, Fibrosis-4 index>3.25, estimated glomerular filtration rate<60, smoking, hypertension, HDL cholesterol and low-density lipoprotein cholesterol, triglycerides, statin prescription, cocaine use, and alcohol use. Adjustment covariates were selected based on previous work suggesting an association with BMI, and IL-6, sCD14, or D-dimer, but adjustment for sex was not possible because of the small number of obese HIV+ women in the cohort.[27] Odds ratios (ORs) for the different categories of the BMI/HIV status variable were compared using Wald tests with a Bonferroni correction for multiple comparisons. We conducted 3 sensitivity analyses: (1) models subcategorizing HIV+ by HIV-1 RNA <500 copies/mL vs ≥500 copies/mL to determine the impact that uncontrolled HIV viremia may have on the association between the inflammatory parameters and BMI status; (2) models excluding those with hepatitis C infection because of its known association with increases in inflammatory biomarkers,[48] and (3) models excluding those with prevalent diabetes, CVD, and cancer, all comorbidities likely to confound the relationship between obesity/HIV comorbidity and IL-6, sCD14, or D-dimer.

RESULTS

Study Population

Of participants included in this cohort, 1477 HIV+ and 823 uninfected participants met the inclusion criteria for this analysis. Of the 68 who were excluded, most (70%) were for being underweight BMI (<18.5 kg/m^2). Of 2300 participants overall, 95% were men; 68% were African American, 37% normal weight, 36% overweight, and 27% obese (Table 1).

Compared with nonobese participants, obese participants had higher prevalence of diabetes, statin prescription, and hypertension, and lower prevalence of alcohol use disorder and current smoking, regardless of HIV status ($P < 0.05$, Table 1). Obese/HIV+ participants had the highest prevalence of HDL <40 mg/dL and triglycerides ≥200 mg/dL ($P < 0.05$, Table 1).

HIV+ participants were less likely to be obese (39%) compared with uninfected participants (61%, $P < 0.001$) and were younger (mean 52 years, SD 8 years) than uninfected participants (54 years, SD 9 years, $P < 0.001$). Of the HIV+ participants, 43% had HIV-1 RNA <500 copies/mL, and 23% had $CD4^+$ cell counts >500 cells/mm^3 at baseline.

Analysis of Inflammatory Biomarkers by Obesity/HIV Status

Median IL-6 levels were significantly higher in obese/HIV+ people (2.26 pg/mL; interquartile range 1.55–3.60) when compared with nonobese/uninfected (1.51 pg/mL; interquartile range: 0.99–2.79; $P < 0.01$; Fig. 1). In unadjusted logistic regression analyses, the odds of elevated IL-6 (ie, being in the highest quartile) were significantly greater in all 3 comparator groups (nonobese/HIV+, obese/uninfected, and obese/HIV+) when compared with the referent (nonobese/uninfected; Table 2). These associations persisted after adjustment for potential confounders: compared with nonobese/uninfected, there were 31% increased odds of elevated IL-6 with HIV infection (nonobese), 64% increased odds with obesity (uninfected), and 79% increased odds with both obesity and HIV (Table 2). Overall, adjusted differences in IL-6 elevation between other pairs of categories (ie, nonobese/HIV+ vs obese/HIV+; or nonobese/HIV+ vs obese/uninfected; or obese/uninfected vs obese/HIV+) were not statistically significant (omnibus $P = 0.11$).

Soluble CD14 levels were significantly lower in obese/HIV+ compared with nonobese/uninfected ($P < 0.01$, Fig. 1). This finding was confirmed in unadjusted and adjusted logistic regression models, where we observed significantly lower odds of elevated sCD14 in obese/HIV+ compared with nonobese/uninfected (both $P < 0.01$; Table 2). Overall differences in sCD14 elevation between other pairs of categories were statistically significant (omnibus $P < 0.001$). This was driven by differences in sCD14 elevation between nonobese/HIV+ vs obese/HIV+ (Bonferroni $P < 0.001$) and obese/uninfected vs obese/HIV+ (Bonferroni $P = 0.02$). Median D-dimer did not differ significantly between BMI/HIV status groups (Fig. 1). This result was reflected in fully adjusted models (Table 2).

Sensitivity analyses that further classified HIV status by HIV-1 RNA < or ≥500 copies/mL demonstrated results consistent with the primary analyses for IL-6 and sCD14 (Table 3). IL-6 and sCD14 levels in nonobese/HIV+ with HIV-1 RNA <500 copies/mL did not differ from those for nonobese/uninfected people, although sample sizes in the subgroups were small (Table 3 footnote). Nonobese/HIV+ people with HIV-1 RNA ≥500 copies/mL had elevated D-dimer relative to nonobese/uninfected people (OR = 1.79; 95% confidence interval = 1.28 to 2.49; Table 3). The same was true for obese/HIV+ people with HIV-1 RNA ≥500 copies/mL, although this association did not reach statistical significance (OR: 1.32; 95% confidence interval = 0.76 to 2.31); Table 3. Two additional sensitivity analyses excluding those with HCV and those with prevalent

TABLE 1. Characteristics of the Cohort Overall and by 4 Obesity/HIV Status Categories: Nonobese HIV Uninfected (Uninfected); Nonobese, Living With HIV (HIV+); Obese/Uninfected; and Obese/HIV+

	Nonobese		Obese		
	Uninfected	HIV+	Uninfected	HIV+	Total
N (% of row)	438 (19)	1232 (54)	385 (17)	245 (11)	2300
Median age (mean, SD), yr	53 (54, 9)	52 (52, 8)	53 (54, 10)	51 (51, 8)	53 (53, 9)
Men	399 (91)	1202 (98)	345 (90)	236 (96)	2182 (95)
Race/ethnicity					
White	85 (19)	244 (20)	88 (23)	37 (15)	454 (20)
African American	309 (71)	836 (68)	241 (63)	179 (73)	1565 (68)
Hispanic	32 (7)	104 (8)	34 (9)	19 (8)	189 (8)
Other	12 (3)	48 (4)	22 (6)	10 (4)	92 (4)
LDL ≥160 mg/dL	28 (6)	60 (5)	29 (8)	13 (5)	130 (6)
HDL <40 mg/dL	111 (25)	511 (41)	165 (43)	128 (52)	915 (40)
Triglycerides ≥200 mg/dL	47 (11)	327 (27)	88 (23)	78 (32)	540 (23)
Total cholesterol ≥200 mg/dL	113 (26)	319 (26)	100 (26)	80 (33)	612 (27)
Statin	156 (36)	356 (29)	202 (52)	99 (40)	813 (35)
FIB-4 index >3.25	21 (5)	109 (9)	11 (3)	16 (7)	157 (7)
eGFR <60 mL·min^{-1}·1.73 m^{-2}	30 (7)	91 (7)	47 (12)	21 (8)	188 (8)
Hemoglobin <12 g/dL	32 (7)	149 (12)	26 (7)	22 (9)	229 (10)
Alcohol use					
Not current	149 (34)	417 (34)	158 (41)	97 (40)	821 (36)
Low risk	65 (15)	278 (23)	78 (20)	61 (25)	482 (21)
At risk/heavy or binge	52 (12)	186 (15)	64 (17)	40 (16)	342 (15)
Abuse/dependence	172 (39)	346 (28)	85 (22)	47 (19)	650 (28)
Smoking					
Nonsmoker	89 (20)	278 (23)	104 (27)	82 (33)	553 (24)
Current smoker	239 (55)	645 (52)	148 (38)	83 (34)	1115 (48)
Past smoker	109 (25)	308 (25)	132 (34)	80 (33)	629 (27)
Cocaine	194 (44)	453 (37)	115 (30)	81 (33)	843 (37)
Hepatitis C	154 (35)	590 (48)	101 (26)	98 (40)	943 (41)
HTN	341 (78)	864 (70)	343 (89)	202 (82)	1750 (76)
CVD	99 (23)	218 (18)	129 (34)	49 (20)	495 (22)
Diabetes	95 (22)	207 (17)	152 (39)	93 (38)	547 (24)
Non–AIDS-defining cancer	28 (6)	58 (5)	28 (7)	12 (5)	12 (5)
AIDS-defining cancer	2 (0.5)	19 (2)	0 (0)	5 (2)	26 (1)
HIV-1 RNA (HIV+ only)					
VL ≥500 copies/mL	0	413 (34)	0	83 (34)	496 (22)
CD4$^+$ Cell Count (HIV+ only)					
CD4 <500 cells/mm^3	0	816 (66)	0	139 (57)	955 (42)

All variables had complete data except the following: LDL cholesterol was available for 2232 participants; HDL for 2240; triglycerides for 2266; total cholesterol for 2279; FIB-4 for 2267; albumin for 2290; eGFR for 2297; alcohol use for 2212; smoking for 2297; HIV-1 RNA for 1476; and CD4 count for 1476 participants.

Data are presented as n and then percent of column in parentheses unless otherwise indicated.

eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 index; HTN, blood pressure ≥ 140/90 or receiving antihypertensive medications; LDL, low-density lipoprotein; statin, HMG-Co-A reductase inhibitor.

diabetes, CVD, and cancer yielded results that were directionally consistent with the primary analyses (Supplemental Digital Content, http://links.lww.com/QAI/B28).

DISCUSSION

In this cross-sectional examination of inflammatory biomarkers in HIV+ and uninfected participants, we found that obesity/HIV comorbidity is associated with elevated IL-6 and decreased sCD14, particularly in the setting of uncontrolled viral replication. Obese/HIV+ participants, when compared with nonobese/uninfected participants, had statistically significant elevations in IL-6, a biomarker of inflammation, and decreases in sCD14, a biomarker of monocyte activation. We did not detect a significant association between obesity/HIV status and D-dimer, a biomarker of altered coagulation.

To our knowledge, this is the largest study comparing IL-6, sCD14, and D-dimer by BMI and HIV status in a cohort including HIV+ and uninfected participants. A recent investigation compared 35 HIV+ with 30 matched, uninfected, obese participants, and found that IL-6 did not significantly differ according to HIV status. They also found sCD14 was

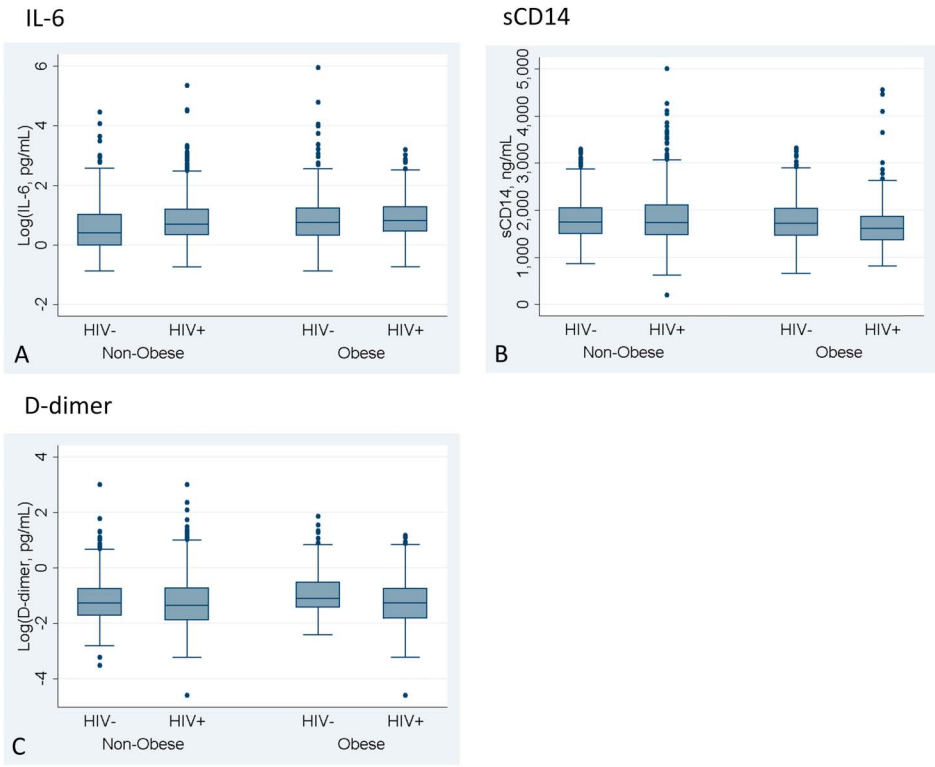

FIGURE 1. Boxplots depicting median, interquartile ranges, and outliers for (A) IL-6, (B) soluble CD14, and (C) D-dimer by obesity/HIV status. A statistically significant difference exists between the nonobese/HIV− and obese/HIV+ groups for log IL-6 ($P < 0.01$) and sCD14 ($P < 0.01$). No significant difference was seen between obesity/HIV status groups for log D-dimer.

increased in obese/HIV+ when compared with obese/uninfected participants, the opposite of the association seen in our study. The characteristics of this smaller cohort differed from those in our cohort in terms of age and gender distributions, and D-dimer levels were not measured.[30]

Multiple prior studies investigated the association between these biomarkers and obesity in HIV+ participants without comparison with an uninfected population. IL-6 did not have a consistent association with adipose tissue mass in HIV+ participants in 1 investigation,[49] whereas in other reports, IL-6 was associated with increases in BMI, particularly for HIV+ men.[31,50] sCD14 was found to increase with weight gain in virologically suppressed, predominately normal weight HIV+ participants between

TABLE 2. Association Between Obesity/HIV Comorbidity and Elevated Biomarkers of Inflammation, Monocyte activation, and Altered Coagulation

		Elevated Biomarker (ie, Highest Quartile), OR (95% CI)					
		IL-6		sCD14		D-dimer	
Logistic Regression Model	**Obesity/HIV Status**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Unadjusted	Nonobese, uninfected	1 (ref)	0.03	1 (ref)	<0.01	1 (ref)	0.03
	Nonobese, HIV+	**1.32 (1.01 to 1.73)**		1.15 (0.90 to 1.49)		1.04 (0.81 to 1.35)	
	Obese, uninfected	**1.54 (1.11 to 2.13)**		0.92 (0.66 to 1.27)		**1.48 (1.09 to 2.03)**	
	Obese, HIV+	**1.59 (1.10 to 2.29)**		**0.58 (0.38 to 0.87)**		0.99 (0.68 to 1.44)	
Age, race/ethnicity adjusted	Nonobese, uninfected	1 (ref)	0.02	1 (ref)	<0.01	1 (ref)	0.04
	Nonobese, HIV+	**1.39 (1.06 to 1.82)**		1.19 (0.92 to 1.53)		1.12 (0.86 to 1.45)	
	Obese, uninfected	**1.55 (1.11 to 2.15)**		0.91 (0.65 to 1.26)		**1.54 (1.12 to 2.11)**	
	Obese, HIV+	**1.71 (1.18 to 2.47)**		**0.61 (0.40 to 0.91)**		1.07 (0.73 to 1.56)	
Fully adjusted	Nonobese, uninfected	1 (ref)	0.02	1 (ref)	<0.01	1 (ref)	0.10
	Nonobese, HIV+	1.30 (0.97 to 1.74)		0.99 (0.75 to 1.30)		1.02 (0.76 to 1.35)	
	Obese, uninfected	**1.63 (1.14 to 2.32)**		0.77 (0.54 to 1.10)		1.38 (0.99 to 1.94)	
	Obese, HIV+	**1.76 (1.18 to 2.63)**		**0.44 (0.28 to 0.69)**		0.91 (0.60 to 1.36)	

Differences significant at $P < 0.05$ are in bold.
Fully adjusted models adjusted for age, race/ethnicity, LDL, HDL, statin use, FIB-4, eGFR, alcohol use, smoking, cocaine use, HCV, HTN, CVD, and diabetes.
IL-6: n = 2227; sCD14 N = 2289; D-dimer N = 2290.
CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 index; LDL, low-density lipoprotein.

TABLE 3. Association Between Obesity/HIV (Subclassified by HIV-1 RNA Status) Comorbidity and Elevated Biomarkers of Inflammation, Monocyte Activation, and Altered Coagulation

			Elevated Biomarker (ie, Highest Quartile), OR (95% CI)					
			IL-6		sCD14		D-Dimer	
Logistic Regression Model	Obesity/HIV Status	HIV-1 RNA (Copies/mL)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Unadjusted	Nonobese, uninfected	—	1 (ref)	<0.01	1 (ref)	<0.01	1 (ref)	<0.01
	Obese, uninfected	—	**1.54 (1.11 to 2.13)**		0.92 (0.66 to 1.27)		**1.48 (1.09 to 2.03)**	
	Nonobese, HIV+	<500	1.06 (0.79 to 1.42)		1.07 (0.81 to 1.40)		0.74 (0.56 to 0.99)	
		≥500	**1.92 (1.40 to 2.63)**		1.33 (0.98 to 1.81)		**1.80 (1.33 to 2.43)**	
	Obese, HIV+	<500	**1.67 (1.10 to 2.53)**		0.63 (0.40 to 1.01)		0.75 (0.47 to 1.19)	
		≥500	1.46 (0.85 to 2.51)		**0.48 (0.24 to 0.94)**		1.56 (0.93 to 2.61)	
Age, race/ethnicity adjusted	Nonobese, uninfected	—	1 (ref)	<0.01	1 (ref)	<0.01	1 (ref)	<0.01
	Obese, uninfected	—	**1.55 (1.11 to 2.15)**		0.91 (0.65 to 1.26)		**1.54 (1.12 to 2.12)**	
	Nonobese, HIV+	<500	1.09 (0.81 to 1.46)		1.07 (0.82 to 1.41)		0.77 (0.58 to 1.03)	
		≥500	**2.16 (1.57 to 2.98)**		**1.45 (1.07 to 1.98)**		**2.06 (1.51 to 2.81)**	
	Obese, HIV+	<500	**1.78 (1.17 to 2.70)**		0.65 (0.41 to 1.05)		0.81 (0.51 to 1.29)	
		≥500	1.65 (0.96 to 2.86)		0.53 (0.27 to 1.04)		**1.75 (1.04 to 2.96)**	
Fully adjusted	Nonobese, uninfected	—	1 (ref)	<0.01	1 (ref)	<0.01	1 (ref)	<0.01
	Obese, uninfected	—	**1.60 (1.13 to 2.28)**		0.77 (0.54 to 1.09)		1.36 (0.97 to 1.90)	
	Nonobese, HIV+	<500	1.05 (0.76 to 1.44)		0.90 (0.67 to 1.21)		0.73 (0.53 to 1.00)	
		≥500	**1.88 (1.33 to 2.66)**		1.17 (0.84 to 1.64)		**1.79 (1.28 to 2.49)**	
	Obese, HIV+	<500	**1.89 (1.21 to 2.96)**		**0.48 (0.29 to 0.80)**		0.72 (0.44 to 1.17)	
		≥500	1.56 (0.86 to 2.82)		**0.38 (0.19 to 0.78)**		1.32 (0.76 to 2.31)	

Differences significant at $P < 0.05$ are in bold.

Fully adjusted models adjusted for age, race/ethnicity, LDL, HDL, statin use, FIB-4, eGFR, alcohol use, smoking, cocaine use, HCV, HTN, CVD, and diabetes.

Sample size within obesity/HIV/HIV-1 RNA (above or below 500 copies/mL) strata: Nonobese HIV uninfected (438), obese HIV uninfected (385), nonobese HIV+ <500 (819), nonobese HIV+ ≥500 (413), obese HIV+ <500 (161), and obese HIV+ ≥500 (83).

CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 index; LDL, low-density lipoprotein.

0 and 48 weeks after antiretroviral initiation across 9 countries.[29] In the Strategies for Management of Antiretroviral Therapy (SMART) Study, investigators did not detect an association between obesity and D-dimer in HIV+ participants,[32] similar to our findings. Likewise, D-dimer was not associated with obesity in a cohort of uninfected participants.[33] These studies, which did not compare HIV+ with uninfected participants in the same cohort, have limited ability to comment on the differential impact of obesity on these biomarkers in those living with HIV versus without HIV infection.

Interleukin 6

We found that obesity and HIV infection contributed to elevations in IL-6, an inflammatory cytokine strongly associated with morbidity and mortality in HIV+ cohorts.[51–55] Median IL-6 levels were significantly higher in obese/HIV+, when compared with nonobese/uninfected, but there was no statistical difference between IL-6 levels in obese/HIV+ and those with either condition alone (nonobese/HIV+ or obese/uninfected, Fig. 1). Thus, we did not find evidence for a synergistic effect of HIV/obesity comorbidity on IL-6 elevations.

Obesity without HIV and HIV viremia without obesity were each associated with IL-6 elevation, and obese/uninfected individuals were more likely to have elevated IL-6 levels than nonobese/uninfected in all 3 logistic regression models. Interestingly, nonobese/HIV+ individuals with HIV-1 RNA <500 copies/mL had similar IL-6 levels to nonobese/uninfected (Table 3), implying that controlled HIV disease alone, without obesity, is not associated with significant elevations in IL-6 in this cohort. Although obese/HIV+ participants with HIV-1 RNA ≥500 copies/mL had a higher prevalence of elevated IL-6 than nonobese/uninfected, this association did not reach statistical significance. The anticipated elevation of IL-6 derived from uncontrolled viral replication may have been present, but the small sample size of only 83 obese/HIV+ participants with HIV-1 RNA ≥500 copies/mL may have limited our ability to detect an association.

The source of IL-6 in obesity/HIV comorbidity may be an important consideration in defining the implications of and future hypotheses generated from our findings. IL-6 can be derived from activated macrophages in tissues, such as blood vessels, or it can be produced by adipocytes, where levels increase in association with adipocyte diameter.[56–58] In obesity, IL-6 is predominately adipose tissue derived, which may differ from chronic HIV infection, where it is likely induced by immune cell activation. Whether (1) adipocyte-derived IL-6 has more local effects on tissues while IL-6 production from immune cell activation has more systemic effects and whether (2) the distribution of local versus systemic effects has impact on morbidity or mortality are important questions for future research.

Soluble CD14

We observed lower sCD14 levels in obese/HIV+ participants compared with nonobese/HIV+ participants, which is in line with results from some previous studies.[45,47,58] Other studies have focused on the association between HIV status and sCD14 elevation in normal weight participants and found increased sCD14 in HIV+ participants.[59–61] A possible explanation for these discordant findings is that hepatic steatosis in obesity leads to lower sCD14 levels because of decreases in hepatocyte-derived sCD14.[62] When HIV and obesity co-occur, sCD14 levels may be influenced by multiple factors including monocyte activation within adipose tissue, other co-occurring inflammatory conditions (eg, diabetes, hepatitis C), and the presence of hepatic steatosis.[63,64] The etiology of the unanticipated findings that sCD14 decreases in the setting of obesity/HIV comorbidity deserve further exploration, and other biomarkers of monocyte activation, such as soluble CD163 or macrophage inflammatory protein-1α, should be examined to determine whether they follow a similar trend.[45] Other illustrative lines of research would repeat this study accounting for differences in hepatic steatosis between groups.

D-Dimer

In fully adjusted models, obesity/HIV comorbidity was not associated with D-dimer except when HIV status was stratified by viral suppression (ie, HIV-1 RNA less or greater than 500 copies/mL). Unsuppressed HIV viremia was associated with increased D-dimer, although this was only statistically significant among nonobese people. The positive association between obesity and D-dimer among HIV-uninfected people did not reach statistical significance. Overall, we did not detect a synergistic effect of obesity/HIV comorbidity on D-dimer elevations.

There are limitations to this analysis. This is an observational, cross-sectional study, preventing us from examining trends over time in inflammatory parameters. It would be useful to examine trends in relation to the duration of virologic suppression or in the setting of weight change or aging. BMI is used as a measure of adiposity rather than a measurement of waist circumference or visceral adipose tissue, known to be more strongly correlated with cardiovascular outcomes. The population is overwhelmingly male and older, limiting generalizability to women and younger HIV+ people. The individual biomarkers measured may not capture the full complexity of the immune processes they represent, although all 3 are well studied in both HIV+ and uninfected cohorts. Data on diet and physical activity, which can confound associations of obesity with inflammatory biomarkers, were not included in this analysis. As with any observational study, there is the possibility of unmeasured confounding from drug use, multiple comorbidities, or other factors.

In summary, obesity/HIV comorbidity is associated with elevated IL-6 and decreased sCD14. However, we did not detect a synergistic effect of obesity/HIV comorbidity on IL-6, sCD14, or D-dimer. This may suggest overlap in the mechanisms by which obesity and HIV contribute to alterations in these biomarkers and the immune processes they represent. The clinical implications of these findings deserve further exploration, as the impact of obesity on morbidity and mortality in HIV+ individuals remains unclear. Recent studies from the North American AIDS Cohort Collaboration on Research and Design suggest that weight gain and obesity are associated with improved $CD4^+$ cell recovery and decreased incidence of noncommunicable diseases.[65,66] However, data from the Data Collection on Adverse Events of Anti-HIV Drugs cohort study show that short-term weight gain after ART initiation, particularly in those with a normal baseline BMI, was associated with increased risk of incident CVD and diabetes.[67]

Despite uncertainty surrounding the impact of rising BMI in this population, the difference in median IL-6 levels between obese/HIV+ and nonobese/uninfected participants our analysis is similar to or greater than differences associated with increased mortality risk in other prospective studies.[53,54] As obesity prevalence among people living with HIV rises,[17] further investigation into the long-term implications of this weight gain is needed. Future prospective studies should assess whether intentional weight loss or similar interventions affect inflammatory processes similarly in HIV-infected and uninfected people.[68–70]

REFERENCES

1. Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000. *JAMA*. 2004;291:1238–1245.
2. Flegal KM, Graubard BI, Williamson DF, et al. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2007;298:2028–2037.
3. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309:71–82.
4. Ogden CL, Carroll MD, Kit BK, et al. *Prevalence of Obesity in the United States, 2009–2010. in: National Center for Health Statistics Data Brief No. 82*. Hyattsville, MD: National Center for Health Statistics; 2012.
5. Wang Y, Beydoun MA. The obesity epidemic in the United States–gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev*. 2007; 29:6–28.
6. Centers for Disease Control and Prevention (CDC). Vital signs: state-specific obesity prevalence among adults—United States, 2009. *MMWR Morb Mortal Wkly Rep*. 2010;59:951–955.
7. Robert SA, Reither EN. A multilevel analysis of race, community disadvantage, and body mass index among adults in the US. *Soc Sci Med*. 2004;59:2421–2434.
8. Zhang Q, Wang Y. Trends in the association between obesity and socioeconomic status in U.S. adults: 1971 to 2000. *Obes Res*. 2004;12: 1622–1632.
9. Zhang Q, Wang Y. Socioeconomic inequality of obesity in the United States: do gender, age, and ethnicity matter? *Soc Sci Med*. 2004;58: 1171–1180.
10. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006–2009. *PLoS One*. 2011;6:e17502.
11. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA*. 2008;300:520–529.
12. Tate T, Willig AL, Willig JH, et al. HIV infection and obesity: where did all the wasting go? *Antivir Ther*. 2012;17:1281–1289.
13. Crum-Cianflone N, Roediger MP, Eberly L, et al. Increasing rates of obesity among HIV-infected persons during the HIV epidemic. *PLoS One*. 2010;5:e10106.
14. Amorosa V, Synnestvedt M, Gross R, et al. A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia. *J Acquir Immune Defic Syndr*. 2005;39:557–561.

15. Koethe JR, Jenkins CA, Shepherd BE, et al. An optimal body mass index range associated with improved immune reconstitution among HIV-infected adults initiating antiretroviral therapy. *Clin Infect Dis.* 2011;53: 952–960.
16. Taylor BS, Liang Y, Garduno LS, et al. High risk of obesity and weight gain for HIV-infected uninsured minorities. *J Acquir Immune Defic Syndr*. 2014;65:e33–40.
17. Koethe JR, Jenkins CA, Lau B, et al. Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. *AIDS Res Hum Retroviruses.* 2016;32:50–58.
18. McGee DL, Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol.* 2005;15:87–97.
19. Arnlov J, Ingelsson E, Sundstrom J, et al. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation*. 2010;121:230–236.
20. Lavie CJ, McAuley PA, Church TS, et al. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol.* 2014;63:1345–1354.
21. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013;173:614–622.
22. Paisible AL, Chang CC, So-Armah KA, et al. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. *J Acquir Immune Defic Syndr.* 2015;68:209–216.
23. Panagiotakos DB, Pitsavos C, Yannakoulia M, et al. The implication of obesity and central fat on markers of chronic inflammation: the ATTICA study. *Atherosclerosis*. 2005;183:308–315.
24. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006; 444:860–867.
25. Amirayan-Chevillard N, Tissot-Dupont H, Capo C, et al. Impact of Highly Active Anti-Retroviral Therapy (HAART) on cytokine production and monocyte subsets in HIV-infected patients. *Clin Exp Immunol.* 2000;120:107–112.
26. Neuhaus J, Jacobs DR Jr, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis.* 2010;201:1788–1795.
27. Armah KA, McGinnis K, Baker J, et al. HIV status, burden of comorbid disease, and biomarkers of inflammation, altered coagulation, and monocyte activation. *Clin Infect Dis.* 2012;55:126–136.
28. Triant VA, Meigs JB, Grinspoon SK. Association of C-reactive protein and HIV infection with acute myocardial infarction. *J Acquir Immune Defic Syndr.* 2009;51:268–273.
29. Mave V, Erlandson KM, Gupte N, et al. Inflammation and change in body weight with antiretroviral therapy initiation in a multinational cohort of HIV-infected adults. *J Infect Dis.* 2016;214:65–72.
30. Koethe JR, Grome H, Jenkins CA, et al. The metabolic and cardiovascular consequences of obesity in persons with HIV on long-term antiretroviral therapy. *AIDS*. 2016;30:83–91.
31. Borges AH, O'Connor JL, Phillips AN, et al. Factors associated with plasma IL-6 levels during HIV infection. *J Infect Dis*. 2015;212: 585–595.
32. Borges AH, O'Connor JL, Phillips AN, et al. Factors associated with D-dimer levels in HIV-infected individuals. *PLoS One*. 2014;9:e90978.
33. Orenes-Pinero E, Pineda J, Roldan V, et al. Effects of body mass index on the lipid profile and biomarkers of inflammation and a fibrinolytic and prothrombotic state. *J Atheroscler Thromb.* 2015;22:610–617.
34. Justice AC, Dombrowski E, Conigliaro J, et al. Veterans Aging Cohort Study (VACS): overview and description. *Med Care.* 2006;44(8 suppl 2): S13–S24.
35. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The cardiovascular health study. *Ann Epidemiol.* 1995;5:278–285.
36. Every NR, Fihn SD, Sales AE, et al. Quality enhancement research initiative in ischemic heart disease: a quality initiative from the department of veterans affairs. QUERI IHD executive Committee. *Med Care.* 2000;38(6 suppl 1):I49–I59.
37. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and Treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252.
38. Armah KA, Chang CC, Baker JV, et al. Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans. *Clin Infect Dis.* 2014;58:121–129.
39. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al. HIV infection and the risk of diabetes mellitus. *AIDS.* 2009;23:1227–1234.
40. McGinnis KA, Brandt CA, Skanderson M, et al. Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. *Nicotine Tob Res.* 2011;13:1233–1239.
41. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;285:2486–2497.
42. Bush K, Kivlahan DR, McDonell MB, et al. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med.* 1998;158:1789–1795.
43. Butt AA, Xiaoqiang W, Budoff M, et al. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis.* 2009;49:225–232.
44. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43:1317–1325.
45. Loko MA, Castera L, Dabis F, et al. Validation and comparison of simple noninvasive indexes for predicting liver fibrosis in HIV-HCV-coinfected patients: ANRS CO3 Aquitaine cohort. *Am J Gastroenterol.* 2008;103: 1973–1980.
46. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 suppl 1):S1–S266.
47. Park LS, Tate JP, Rodriguez-Barradas MC, et al. Cancer incidence in HIV-infected versus uninfected veterans: comparison of cancer Registry and ICD-9 code diagnoses. *J AIDS Clin Res.* 2014;5:1000318.
48. Armah KA, Quinn EK, Cheng DM, et al. Human immunodeficiency virus, hepatitis C, and inflammatory biomarkers in individuals with alcohol problems: a cross-sectional study. *BMC Infect Dis.* 2013;13:399.
49. Koethe JR, Dee K, Bian A, et al. Circulating interleukin-6, soluble CD14, and other inflammation biomarker levels differ between obese and nonobese HIV-infected adults on antiretroviral therapy. *AIDS Res Hum Retroviruses.* 2013;29:1019–1025.
50. Conley LJ, Bush TJ, Rupert AW, et al. Obesity is associated with greater inflammation and monocyte activation among HIV-infected adults receiving antiretroviral therapy. *AIDS*. 2015;29:2201–2207.
51. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med.* 2008;5:e203.
52. Duprez DA, Neuhaus J, Kuller LH, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. *PLoS One*. 2012;7:e44454.
53. Nordell AD, McKenna M, Borges AH, et al. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. *J Am Heart Assoc.* 2014;3:e000844.
54. McDonald B, Moyo S, Gabaitiri L, et al. Persistently elevated serum interleukin-6 predicts mortality among adults receiving combination antiretroviral therapy in Botswana: results from a clinical trial. *AIDS Res Hum Retroviruses.* 2013;29:993–999.
55. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity*. 2013;39:633–645.
56. Tanaka T, Kishimoto T. The biology and medical implications of interleukin-6. *Cancer Immunol Res.* 2014;2:288–294.
57. Skurk T, Alberti-Huber C, Herder C, et al. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab.* 2007;92:1023–1033.
58. Jernas M, Palming J, Sjoholm K, et al. Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression. *FASEB J.* 2006;20:1540–1542.
59. Cassol E, Malfeld S, Mahasha P, et al. Persistent microbial translocation and immune activation in HIV-1-infected South Africans receiving combination antiretroviral therapy. *J Infect Dis.* 2010;202:723–733.
60. Lien E, Aukrust P, Sundan A, et al. Elevated levels of serum-soluble CD14 in human immunodeficiency virus type 1 (HIV-1) infection: correlation to disease progression and clinical events. *Blood*. 1998;92: 2084–2092.
61. Wallet MA, Rodriguez CA, Yin L, et al. Microbial translocation induces persistent macrophage activation unrelated to HIV-1 levels or T-cell activation following therapy. *AIDS*. 2010;24:1281–1290.

62. du Plessis J, Korf H, van Pelt J, et al. Pro-inflammatory cytokines but not endotoxin-related parameters associate with disease severity in patients with NAFLD. *PLoS One*. 2016;11:e0166048.
63. Quon BS, Ngan DA, Wilcox PG, et al. Plasma sCD14 as a biomarker to predict pulmonary exacerbations in cystic fibrosis. *PLoS One*. 2014;9: e89341.
64. Bas S, Gauthier BR, Spenato U, et al. CD14 is an acute-phase protein. *J Immunol.* 2004;172:4470–4479.
65. Koethe JR, Jenkins CA, Lau B, et al. Body mass index and early CD4 T-cell recovery among adults initiating antiretroviral therapy in North America, 1998–2010. *HIV Med.* 2015;16:572–577.
66. Koethe JR, Jenkins CA, Lau B, et al. Higher time-updated body mass index: association with improved CD4+ cell recovery on HIV treatment. *J Acquir Immune Defic Syndr.* 2016;73:197–204.
67. Achhra AC, Mocroft A, Reiss P, et al. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. *HIV Med.* 2016;17:255–268.
68. Fitch K, Abbara S, Lee H, et al. Effects of lifestyle modification and metformin on atherosclerotic indices among HIV-infected patients with the metabolic syndrome. *AIDS*. 2012;26:587–597.
69. Lindegaard B, Hansen T, Hvid T, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. *J Clin Endocrinol Metab.* 2008;93:3860–3869.
70. Troseid M, Ditlevsen S, Hvid T, et al. Reduced trunk fat and triglycerides after strength training are associated with reduced LPS levels in HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2014; 66:e52–e54.