Relationship of visceral and subcutaneous adipose depots to markers of arterial injury and inflammation among individuals with HIV

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Objective: Persons living with HIV (PLWH) well treated on antiretroviral therapies remain at risk for ensuing arterial disease. We investigated the relationship between adipose depots and biomarkers of arterial injury and inflammation to gain insight into the link between body composition and CVD risk.

Designs/methods: One hundred and fifty-five HIV-infected and 70 non-HIV infected individuals were well phenotyped for body composition. Adipose depots were assessed via single-slice abdominal computed tomography (CT). Circulating markers of arterial disease and generalized inflammation [lipoprotein-associated phospholipase A2 (LpPLA2), oxidized low-density lipoprotein (oxLDL), high-sensitivity cardiac troponin T (hs-cTnT), high-sensitivity C-reactive protein (hsCRP)] were evaluated.

Results: Despite similar BMI and visceral adipose tissue (VAT), HIV-infected individuals had significantly lower subcutaneous adipose tissue [SAT, 199 (126–288) vs. 239 (148–358) cm^2, $P = 0.04$] than non-HIV infected individuals. Among HIV-infected individuals, reduced SAT inversely correlated with LpPLA2 ($\rho = -0.19$, $P = 0.02$) and hs-cTnT ($\rho = -0.24$, $P = 0.004$), whereas increased VAT significantly and positively related to LpPLA2 ($\rho = 0.25$, $P = 0.003$), oxLDL ($\rho = 0.28$, $P = 0.0005$), hs-cTnT ($\rho = 0.28$, $P = 0.0007$) and hsCRP ($\rho = 0.32$, $P = < 0.0001$). Similar analyses among the non-HIV infected individuals revealed significant relationships between SAT and LpPLA2 ($\rho = -0.24$, $P = 0.05$), as well as VAT and LpPLA2 ($\rho = 0.37$, $P = 0.002$), oxLDL ($\rho = 0.24$, $P = 0.05$) and hsCRP ($\rho = 0.29$, $P = .02$). In modelling performed among the HIV group, simultaneously controlling for VAT, SAT, age and relevant HIV-related parameters, reduced SAT was an independent predictor of LpPLA2 ($P = 0.04$) and hs-cTnT ($P = 0.005$) and increased VAT was an independent predictor of LpPLA2 ($P = 0.001$), oxLDL ($P = 0.02$), hs-cTnT ($P = 0.04$) and hsCRP ($P = 0.04$).

Conclusion: Fat redistribution phenotypes, characterized by SAT loss and/or VAT accumulation, may be linked to arterial injury and inflammation in HIV.

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Introduction

Persons living with HIV (PLWH) well treated on antiretroviral therapies (ARTs) remain at an increased risk for arterial disease, including atherosclerotic plaque formation [1–4], as compared with persons living without HIV (PLWOH). Inflammation plays an integral role in the underlying pathogenesis for atherosclerotic disease, as circulating monocytes adhere to the vascular endothelium and differentiate into macrophages within the intima. Low-density lipoprotein (LDL) particles are engulfed by these macrophages potentiating the formation of lipid-laden foam cells, which are the nidus of atheroma progression. Even in the setting of good virologic control and contemporary ART use, PLWH demonstrate chronic immune activation and systemic inflammation [2,5,6], which has critical implications for cardiovascular risk [7].

Circulating markers of inflammation have been identified to be useful in risk stratification of cardiovascular disease (CVD) and arterial disease. Lipoprotein-associated phospholipase A2 (LpPLA2) may be a useful marker of arterial inflammation, as it is recognized to be released from rupture-prone arterial plaque [8–10]. LpPLA2 functions to oxidize phospholipids found on LDL particles within the arterial intima. Oxidation of LDL more readily occurs in a pro-inflammatory milieu and is an important mechanism of plaque formation. Subclinical arterial plaque deposition may have further consequences, inciting myocardial injury, which can be assessed by high-sensitivity cardiac troponin T (hs-cTnT). Indices of arterial inflammation and subclinical atherosclerosis are increased in HIV [8,11], and the systemic mechanisms that may contribute to an increased CVD risk in this population remain unclear.

Among PLWH, adipose dysfunction remains prevalent, whether related to ARTs or the virus itself [12] or the ageing process. In this regard, unfavourable changes in fat redistribution, including visceral adipose tissue (VAT) accumulation and subcutaneous adipose tissue (SAT) loss, demonstrated among PLWH have been linked to adipose dysfunction and may contribute to a highly inflamed phenotype with broader immunomodulatory effects. In the context of fat redistribution and adipose dysfunction, localized inflammation within the adipose depot could potentially contribute to systemic inflammation through paracrine activity. In the current study, we investigated for the first time the relationship between body composition, specifically related to the visceral and subcutaneous depots, and specific biomarkers of arterial injury and inflammation to gain insight into the potential link between adiposity and CVD risk in HIV. We hypothesized that markers of arterial disease and generalized inflammation would be increased in relation to VAT accumulation and SAT loss, a metabolic phenotype and pattern of fat redistribution associated with pronounced inflammation in the HIV population.

Materials and methods

Study participants

One hundred and fifty-five HIV-infected and 70 non-HIV infected individuals were previously recruited between 2006 and 2011. HIV-infected individuals were recruited from HIV medical clinics and community health centres and through newspaper advertisements in the Boston area. Non-HIV infected individuals were similarly recruited from the identical communities using the same advertisements. Individuals were included in the HIV group if there was a known history of HIV for more than 5 years. No changes to ART regimens were allowed within the past 3 months. Data on ART use were collected by self-report. Aside from HIV serostatus and ART use, inclusion and exclusion criteria were similar for both groups. Individuals were between 18 and 60 years of age with a BMI between 20 and 35 kg/m^2 and had no known cardiac disease. Active use of anti-inflammatory medications was not permitted. Individuals were excluded for any acute infectious illness. All participants provided informed consent to participate. This study was approved by the institutional review board of Massachusetts General Hospital. Data relevant to coronary artery disease have been previously reported in this cohort [1,2,11,13], whereas data on body composition and arterial injury and inflammation are the focus of the current study.

Evaluation of body composition

The waist-to-hip ratio was assessed by dividing the iliac waist circumference by the circumference at the broadest part of the hip. To assess abdominal VAT and SAT area, a cross-sectional computed tomography (CT) scan at the level of the L4 pedicle was performed. Scan parameters for each image were standardized (144 table height, 80 kV, 70 mA, 2 s, 10 mm slice thickness, 48 cm FOV). Fat attenuation coefficients were set at −50 to −250 HU. Following image acquisition, an offline analysis of tracings was performed utilizing commercial software (Vitrak, Merge e/Film; Chicago, Illinois, USA) to quantitate abdominal VAT and SAT area.

Circulating markers of arterial disease and generalized inflammation

During the study, samples were collected and stored frozen at -80°C. Markers were assessed after the completion of the study. LpPLA2 was measured using activity assay reagents (Diadexus, South San Francisco, California, USA) on a Vista Dimension 1500 system (Siemens Healthcare Diagnostics, Glasgow, Delaware, USA). LpPLA2 assay specifics include a measurement range 10–400 nmol/min per ml and interassay coefficients of variation 1.7–3.2% at values between 97 and 304 nmol/min per ml. Hs-cTnT was evaluated via the Cobas e601 instrument system (Roche Diagnostics, Indianapolis, Indiana, USA). Hs-cTnT assay specifics include a measurement range 3.0–10 000 ng/l and interassay coefficients of variation 3.6 to 2.3% at values between 28 and 4962 ng/l. For values below the limit of

detection for the hs-cTnT assay, imputed values just below the limit of detection were used for purposes of data analysis (i.e. hs-cTnT 2.99 ng/l. Oxidized LDL (oxLDL) was measured by ELISA as per manufacturer instructions (Mercodia, Uppsala, Sweden). Assay specifics for oxLDL include a measurement range of 8–150 U/l and interassay coefficients of variation ranged from 8.3 to 7.4% at values between 8.5 and 32 U/l. High sensitivity C-reactive protein (hsCRP) was assessed using ELISA (LabCorp, Cranford, New Jersey, USA).

HIV-specific parameters

HIV viral load was determined by ultrasensitive RT PCR (Roche COBAS Amplicor; Pleasanton, California, USA) (lower limit of detection, 50 copies/ml). For values below the limit of detection, imputed values just below the limit of detection were used for purposes of data analysis (i.e. viral load 49 copies/ml). $CD4^+$ and $CD8^+$ T cell counts were assessed by flow cytometry.

Statistical analysis

Normality of distribution was assessed using the Shapiro–Wilks test. Data are presented as mean ± standard deviation if normally distributed or median (IQR) if not normally distributed. Categorical variables are reported as proportions. Between-group comparisons (HIV vs. non-HIV) were made using the Student's *t*-test for normally distributed variables or Wilcoxon Rank Sums test for nonnormally distributed variables. Spearman's correlation coefficient was used to perform linear regression to relate body composition to markers of arterial injury and inflammation by HIV status. Multivariate regression was performed among the HIV group to assess independent effects of HIV-related parameters and adipose depots on markers of arterial injury and inflammation. VAT and SAT were chosen as independent variables of body composition for the model given the significance of these measures in the univariate modelling and to address the aim of this investigation to assess the contribution of specific adipose depots. Given the importance of viral effects and the ageing process to adipose dysregulation and redistribution as well as chronic inflammation and vascular disease, HIV-related variables, including duration of HIV, duration of ART use, $CD4^+$ nadir count, viral load and age, were entered into the model to determine whether the adipose depots were independently linked to markers of arterial injury and inflammation. In order to perform an ROC analysis, we transformed dependent variables (markers of arterial injury and inflammation) into dichotomous variables using accepted cutoffs or the median value when clinical cutoffs were not available: LpPLA2 more than 200.0 nmol/min per ml (high risk), oxLDL more than 43.9 (median value), hs-cTnT more than 3.00 ng/l (limit of detection), hsCRP more than 3.0 mg/l (high risk). Statistical significance was defined as *P* value less than 0.05. All analyses were performed using SAS JMP (version 12.0; SAS Inc., Cary, North Carolina, USA).

Results

Demographics and clinical characteristics

HIV-infected and non-HIV infected individuals were of similar age (47 ± 7 vs. 46 ± 7 years), race (53 vs. 51% white) and sex (61 vs. 59% male), respectively (all $P > 0.05$). The HIV group demonstrated a history of infection for 14 ± 6 years, a duration of ART use for 8 ± 5 years and good immunological parameters with $CD4^+$ cell count 552 ± 290 cells/μl and $\log_{10}$ viral load 1.82 ± 0.49 copies/ml (Table 1).

A modest percentage of HIV-infected individuals self-reported prior use of zidovudine (47.7%) or stavudine (22.6%), and current use of zidovudine (10.3%) or stavudine (1.9%) was reported by even fewer.

Assessment of body composition and metabolic parameters

Despite similar BMI (27 ± 5 vs. 27 ± 5 kg/m^2, $P = 0.31$), waist to hip ratio (0.94 ± 0.07 vs. 0.92 ± 0.07, $P = 0.19$) and VAT [109 (61–210) vs. 103 (54–174) cm^2, $P = 0.35$], HIV-infected individuals had significantly lower SAT [199 (126–288) vs. 239 (148–358) cm^2, $P = 0.04$] than non-HIV infected individuals. In addition, the VAT to SAT ratio [0.54 (0.30–1.13) vs. 0.42 (0.23–0.79) cm^2, $P = 0.03$] was significantly increased in the HIV vs. non-HIV group. Metabolic parameters, including triglycerides [97 (77–172) vs. 84 (62–121) mg/dl, $P = 0.001$), alanine aminotransferase (ALT) (35 ± 28 vs. 25 ± 17 U/dl, $P = 0.0006$) and aspartate aminotransferase (AST) (39 ± 30 vs. 28 ± 16 U/dl, $P = 0.001$), were significantly higher among HIV vs. non-HIV infected individuals (Table 1).

Markers of arterial disease and generalized inflammation

Hs-cTnT [3.09 (2.99–6.44) vs. 2.99 (2.99–3.00) ng/l, $P = 0.03$] was significantly greater among HIV-infected vs. non-HIV infected individuals. Detectable hs-cTnT values were obtained in 50% of HIV-infected individuals compared with 41% of non-HIV infected individuals. Other markers, such as LpPLA2 [184.2 (152.6–229.7) vs. 173.0 (146.7–216.6) nmol/min/ml, $P = 0.12$], oxLDL [43.9 (33.4–53.5) vs. 44.4 (35.8–56.4) U/l, $P = 0.48$] and hsCRP [1.4 (0.5–3.9) vs. 1.3 (0.5–3.5) cm^2, $P = 0.67$] were similar between the HIV and non-HIV groups as previously reported [11] (Table 1).

Relationship of adipose depots and markers of arterial disease and generalized inflammation among HIV-infected and non-HIV infected individuals

Among HIV-infected individuals, reduced SAT inversely correlated with LpPLA2 ($\rho = -0.19$, $P = 0.02$) and hs-cTnT ($\rho = -0.24$, $P = 0.004$). Increased VAT significantly and positively related to LpPLA2 ($\rho = 0.25$, $P = 0.003$), oxLDL ($\rho = 0.28$, $P = 0.0005$), hs-cTnT ($\rho = 0.28$, $P = 0.0007$) and hsCRP ($\rho = 0.32$, $P \leq 0.0001$) (Table 2). In addition,

Table 1. Baseline demographic and clinical characteristics.

	HIV-infected individuals ($n = 155$)	Non-HIV infected individuals ($n = 70$)	*P*
Demographics			
Age (years)	47 ± 7	46 ± 7	0.17
Race (%)			0.38
White	53	51	
African American	40	37	
Male sex (%)	61	59	0.70
Current tobacco use (%)	44	40	0.56
Current diabetes (%)	10	7	0.43
Current statin use (%)	14	4	0.03
HIV parameters			
$CD4^+$ T cell count (cells/μl)	552 ± 290	N/A	–
$CD4^+$ T cell nadir (cells/μl)	193 ± 164	N/A	–
$CD8^+$ T cell count (cells/μl)	912 ± 486	N/A	–
Log HIV RNA viral load (copies/ml)	1.82 ± 0.49	N/A	–
Undetectable HIV viral load (%)	86%	N/A	–
Duration HIV (years)	14 ± 6	N/A	–
Duration ART use (years)	8 ± 5	N/A	–
Current PI use (%)	55	N/A	–
Current NRTI use (%)	95	N/A	–
Current NNRTI use (%)	37	N/A	–
History of HCV infection (%)[a]	27	9	0.0008
Body composition and metabolic parameters			
BMI (kg/m^2)	27 ± 5	27 ± 5	0.31
Waist to hip ratio	0.94 ± 0.07	0.92 ± 0.07	0.19
SAT (cm^2)	199 (126–288)	239 (148–358)	0.04
VAT (cm^2)	109 (61–210)	103 (54–174)	0.35
VAT to SAT ratio	0.54 (0.30–1.13)	0.42 (0.23–0.79)	0.03
Triglycerides (mg/dl)	97 (77–172)	84 (62–121)	0.001
HDL (mg/dl)	50 (41–62)	49 (42–64)	0.81
LDL (mg/dl)	98 (78–124)	105 (89–127)	0.25
ALT (U/dl)	35 ± 28	25 ± 17	0.0006
AST (U/dl)	39 ± 30	28 ± 16	0.001
Markers of arterial injury and inflammation			
LpPLA2 activity (nmol/min/ml)	184.3 (152.6–229.7)	173.0 (146.7–216.6)	0.12
Oxidized LDL (U/l)	43.9 (33.4–53.5)	44.4 (35.8–56.4)	0.48
hs-cTnT (ng/l)	3.09 (2.99–6.44)	2.99 (2.99–3.99)	0.03
hsCRP (mg/l)	1.4 (0.5–3.9)	1.3 (0.5–3.5)	0.67

Data reported as mean ± standard deviation, percentage or median (interquartile range). ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; HCV, hepatitis C virus; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; LDL, low-density lipoprotein; LpPLA2, lipoprotein-associated phospholipase A2; N/A, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; PI, protease inhibitor; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.
[a]History of HCV infection based on self-report.

Table 2. Correlations of body composition with markers of arterial injury and inflammation.

	LpPLA2 activity (nmol/min/ml)		Oxidizes LDL (U/l)		hs-cTnT (ng/l)		hs-CRP (mg/l)	
	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*
HIV-infected individuals ($n = 155$)								
BMI (kg/m^2)	−0.05	0.50	0.22	0.007	−0.02	0.83	0.36	<0.0001
Waist to hip ratio	0.16	0.06	0.21	0.02	0.24	0.007	0.28	0.002
SAT (cm^2)	−0.19	0.02	0.12	0.16	−0.24	0.004	0.17	0.04
VAT (cm^2)	0.25	0.003	0.28	0.0005	0.28	0.0007	0.32	<0.0001
VAT to SAT ratio	0.38	<0.0001	0.16	0.06	0.40	<0.0001	0.16	0.06
Non-HIV infected individuals ($n = 70$)								
BMI (kg/m^2)	0.03	0.84	0.05	0.71	0.04	0.73	0.18	0.14
Waist to hip ratio	0.32	0.01	0.31	0.01	0.18	0.17	0.24	0.06
SAT (cm^2)	−0.24	0.05	−0.07	0.58	−0.19	0.12	0.15	0.24
VAT (cm^2)	0.37	0.002	0.24	0.05	0.10	0.42	0.29	0.02
VAT to SAT ratio	0.49	<0.0001	0.19	0.12	0.30	0.01	0.20	0.11

Relationships were assessed by Spearman's correlation coefficient. hsCRP, high-sensitivity C-reactive protein; Hs-cTnT, high-sensitivity cardiac troponin T; LDL, low-density lipoprotein; LpPLA2, lipoprotein-associated phospholipase A2; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 3. Model to assess determinants of markers of arterial injury and inflammation among HIV-infected individuals.

	LpPLA2 activity (nmol/min/ml)		Oxidizes LDL (U/l)		hs-cTnT (ng/l)		hs-CRP (mg/l)	
	β estimate	*P*	β estimate	*P*	β estimate	*P*	β estimate	*P*
	($R^2 = 0.20$; $P = 0.02$)		($R^2 = 0.20$; $P = 0.02$)		($R^2 = 0.20$; $P = 0.02$)		($R^2 = 0.20$; $P = 0.02$)	
SAT (cm^2)	−0.0896	0.04	0.0192	0.13	−0.0195	0.005	0.0041	0.20
VAT (cm^2)	0.2194	0.001	0.0478	0.02	0.0212	0.04	0.0103	0.04
Duration of HIV (years)	−0.0842	0.94	0.0905	0.78	0.3214	0.07	−0.2068	0.01
Duration of ART use (years)	1.8323	0.18	0.5445	0.17	−0.1945	0.36	0.1373	0.17
$CD4^+$ nadir count (cells/μl)	−0.0168	0.62	−0.0023	0.82	−0.0060	0.27	−0.0027	0.29
Log_{10} HIV viral load (copies/ml)	−13.8512	0.41	−3.5921	0.46	4.9540	0.06	2.0334	0.10
Age (years)	−0.5370	0.55	−0.0267	0.92	−0.0488	0.73	0.0958	0.15

R^2 represents the coefficient of determination and the proportion of variance explained by the model. *P* value represents significance by the whole model ANOVA test. hsCRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; LDL, low-density lipoprotein; LpPLA2, lipoprotein-associated phospholipase A2; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

LpPLA2 ($\rho = 0.38$, $P \leq 0.0001$) and hs-cTnT ($\rho = 0.40$, $P \leq 0.0001$) demonstrated a significant correlation with the VAT to SAT ratio, while oxLDL ($\rho = 0.16$, $P = 0.06$) and hsCRP ($\rho = 0.16$, $P = 0.06$) tended to be correlated with the VAT to SAT ratio among the HIV group (Table 2).

Similar analyses among non-HIV infected individuals revealed significant relationships between SAT and LpPLA2 ($\rho = -0.24$, $P = 0.05$), as well as VAT and LpPLA2 ($\rho = 0.37$, $P = 0.002$), oxLDL ($\rho = 0.24$, $P = 0.05$) and hsCRP ($\rho = 0.29$, $P = 0.02$). The VAT to SAT ratio was positively correlated to LpPLA2 ($\rho = 0.49$, $P \leq 0.0001$) and hs-cTnT ($\rho = 0.30$, $P = 0.01$) in the non-HIV group (Table 2).

Multivariate regression modelling among HIV-infected individuals to assess effects of HIV and adipose-related indices on markers of arterial disease and generalized inflammation

In separate models controlling for SAT, VAT, age, duration of HIV infection, duration of ART use, nadir $CD4^+$ cell count and viral load among the HIV group, reduced SAT was independently associated with LpPLA2 (β estimate -0.0896, $P = 0.04$) and hs-cTnT (β estimate -0.0195, $P = 0.005$) and increased VAT was independently associated with LpPLA2 (β estimate 0.2194, $P = 0.001$), oxLDL (β estimate 0.0478, $P = 0.02$), hs-cTnT (β estimate 0.0212, $P = 0.04$) and hsCRP (β estimate 0.0103, $P = 0.04$) (Table 3). We determined the AUC for these models after applying an ROC analysis: LpPLA2 (AUC = 0.78, $P = 0.007$), oxLDL (AUC = 0.76, $P = 0.01$), hs-cTnT (AUC = 0.78, $P = 0.004$), hsCRP (AUC = 0.78, $P = 0.03$).

Discussion

We demonstrate that specific measures of fat redistribution relate to markers of arterial disease among HIV-infected individuals well phenotyped for body composition changes. These are the first data among PLWH to relate markers of arterial disease, LpPLA2, oxLDL and hs-cTnT, to the visceral and subcutaneous depots. Specifically, increased VAT and decreased SAT each had distinct associations to these markers in the HIV population, and the regional pattern of fat redistribution may be more critical to ensuing inflammation [14]. Assessment of visceral and subcutaneous distributions, among PLWH, could potentially help discern those who may be at a greater risk for inflammatory-mediated CVD.

PLWH may be predisposed to atrophy of the subcutaneous depot in the setting of toxic ART side effects or direct viral actions on the adipocytes. Shifts in macrophage populations at the tissue level in the context of adipose redistribution, for example in HIV-associated lipoatrophy, may contribute to inflammation in the subcutaneous depot [15]. In support of this hypothesis, prior findings have demonstrated tissue-specific inflammation, and loss of peripheral subcutaneous fat in association with in-situ inflammation utilizing FDG-PET imaging techniques to assess metabolic activity in the fat [16]. Data in the current study now show that reduced SAT may also be related to arterial disease and generalized inflammation, as evidenced by significant inverse relationships to LpPLA2, hs-cTnT and hsCRP, among HIV-infected individuals.

Several more recent studies demonstrate increases in VAT regardless of specific class when initiating contemporary ART [17,18], and SAT loss may have less clinical relevance with use of contemporary regimens. In the current study, approximately one-third of HIV-infected individuals were exposed to prior use of a thymidine analogue. Visceral adiposity is related to increased overall CVD mortality [19], and emerging literature demonstrates that VAT-derived exosomes may promote proatherogenic effects via macrophage foam cell regulation in animal models of obesity [20]. A plausible mechanism for the increased risk of arterial disease in HIV may similarly link the increased pro-inflammatory milieu in expanded VAT to systemic effects on the vasculature.

LpPLA2 is increased in generalized obesity [21], and human adipocytes have been reported to be a source of

LpPLA2 [22]. Moreover, application of a LpPLA2 inhibitor also reduced oxLDL production from human adipocytes [22]. Excess VAT has been correlated with oxLDL among PLWOH [23]. In contrast, few data are available on these markers of arterial disease in relation to body composition among PLWH. Circulating oxLDL has been shown to be increased among those PLWH demonstrating a lipodystrophy phenotype [24], but not related to specific depots as shown by our data in the current study. The relationship of LpPLA2 and hs-cTnT to the visceral and subcutaneous depots has not previously been explored in HIV. Few studies have demonstrated a link between troponin and general body composition (i.e. BMI) among the non-HIV population [25].

Hs-cTnT is a marker of myocardial injury that occurs as a result of ischaemia, which could be precipitated by atherosclerotic plaque, but is not specific to this and could be increased in other CVD states, including reduced coronary flow reserve and heart failure [26–28]. Fat redistribution could be indicative that other ectopic fat depots, such as epicardial, pericardial or perivascular fat, are present in measurable amounts. In this way, reduced SAT and/or excess VAT could be an overall indicator of fat redistribution, and dysfunctional adipose depots closer in proximity to the vasculature and/or myocardium may actually drive increased CVD risk, including both arterial disease, myocardial fibrosis and diastolic dysfunction, the prevalence of which is increased in HIV [2,29].

In the general population without known CVD risk, VAT has been linked to increased arterial inflammation using imaging techniques such as ^{18}FDG-PET/CT [30], a good surrogate for the in-vivo measurement of macrophage activity in the arterial wall which correlates well with circulating inflammatory biomarkers [31]. Prior studies among PLWH have demonstrated that excess VAT and/or reduced SAT relate to indices of CVD, including carotid artery stiffness and presence of coronary plaque among single sex cohorts [32,33]. We now extend this work to show the relative importance of the VAT and VAT/SAT ratio in the HIV population, without known CVD, to broad indices of systemic and arterial injury and inflammation.

In multivariate modelling, we demonstrate that adipose depots may contribute to an inflamed phenotype independent of HIV-related parameters, including duration of HIV infection, duration of ART use, nadir CD4$^+$ cell count and viral load. This is an important observation in the context of a well treated HIV population, and highlights fat redistribution as a potential mechanism for ensuing inflammation despite adequate immunological control. There is emerging evidence to suggest that fat depots serve as a viral reservoirs [34,35]. Localized inflammation within the fat depot originating from pathologic macrophage infiltration may contribute systemically to inflammatory-mediated metabolic complications. Further studies linking in-situ depot-specific tissue inflammation, macrophage infiltration and arterial inflammation will be important to perform.

There are limitations to the current study. The study was cross-sectional in nature, so we cannot fully assess the causality of the relationship between body composition and arterial inflammation. Moreover, we used markers of arterial injury and inflammation as a proxy for CVD. Nonetheless, in a well phenotyped group with significant changes in fat redistribution, we demonstrate consistent links between body composition and arterial injury and inflammation. On the basis of these initial findings, it would be important to assess for changes in fat redistribution longitudinally and determine whether unfavourable changes in the VAT and SAT developing over time contribute to arterial injury and inflammation.

These data are representative of a cohort of long-term survivors who are heavily treatment experienced and may not reflect contemporary populations of PLHIV and the new ART regimens. In addition, specific ART, such as thymidine analogues, may have larger contributions to fat dysfunction and redistribution that could not be individually assessed in the current study. Moreover, with the growing epidemic of obesity in HIV, combined accumulation of VAT and SAT may be another phenotype on the spectrum of body composition changes, which requires further evaluation as a contributor to systemic inflammation and CVD.

In the context of SAT loss and/or VAT accumulation among HIV-infected individuals, dysfunctional and inflamed adipose tissue, may be linked to arterial disease. Circulating biomarkers of arterial injury and inflammation may be useful to identify those with evidence of fat redistribution who may be at risk for CVD. Strategies to restore normal adipose biology and reduce adipose dysfunction may have therapeutic benefit to dampen arterial injury and inflammation in the HIV population among whom traditional risk factor modification does not completely mitigate CVD risk.

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S.S., K.V.L., M.T., R.C., P.M. have nothing to declare. M.V.Z. participated in a Scientific Advisory Board meeting for Roche Diagnostics and received research funding from Gilead Sciences; C.D. received research funding from Roche Diagnostics, served as a consultant for Abbott Diagnostics, FujiRebio, Metanomics, Ortho Diagnostics and Siemens Healthcare, and received honorarium from Medscape and royalties from UpToDate; S.E.L. is a nonpaid Board member of the community nonprofit organization Healing Our Community Collaborative and received one-time compensation for CME educational offerings sponsored by the Association of Nursing in AIDS Care and New England AIDS Education and Training Center; J.L. participated in a Scientific Advisory Board meeting for Gilead Sciences and served as a consultant for Viiv Healthcare; S.K.G. has received research funding from Gilead Sciences, KOWA and Theratechnologies, and served as a consultant for Navidea Inc. and Theratechnologies.

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Conflicts of interest

The authors have no conflicts of interest.

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