Association of epicardial fat with noncalcified coronary plaque volume and with low attenuation plaque in people with HIV

Manel Sadouni[a,b], Madeleine Durand[a,b,c], Irina Boldeanu[d], Coraline Danieli[e], Paule Bodson-Clermont[a], Samer Mansour[a,b,f], Jean-Guy Baril[a,b,g], Benoit Trottier[g], Cécile Tremblay[a,b,h], Carl Chartrand-Lefebvre[a,b,d], for the investigators of the Canadian HIV and Aging Cohort Study

Objectives: People with HIV are exposed to a higher risk of coronary artery disease (CAD) compared with the general population. Epicardial fat may play a unique role in promoting coronary atherosclerosis. We measured epicardial fat in participants living with HIV and controls and investigated its association with coronary plaque volume and low attenuation plaque, a marker of plaque vulnerability.

Design: This is a cross-sectional study, nested in the Canadian HIV and Aging Cohort Study, a large prospective cohort actively following participants with HIV and controls. Participants with low/intermediate cardiovascular risk without symptoms/history of CAD were invited to undergo cardiac computed tomography (CT).

Methods: Volume of epicardial fat, coronary plaque and low attenuation component of the plaque were measured. Association between epicardial fat, coronary plaque volume and low attenuation component was tested using adjusted regression analysis.

Results: A total of 169 participants with HIV and 81 controls underwent cardiac CT. Participants with HIV had a greater epicardial fat volume compared with controls ($P = 0.019$). In participants with HIV, epicardial fat volume was positively associated with duration of nonnucleoside reverse transcriptase inhibitors (NNRTI) (β=2.19, $P = 0.004$). After adjustment for cardiovascular risk factors, epicardial fat volume was positively associated to noncalcified plaque volume [odds ratio (OR) = 1.09, $P = 0.028$] and to the low-attenuation plaque component portion (β=0.38, $P = 0.026$).

Conclusion: The association of epicardial fat volume to noncalcified plaque volume and to low attenuation component plaque may suggest a potential mechanism by which epicardial fat could be a silent driver of CAD in the HIV population.

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[a]Centre hospitalier de l'Université de Montréal (CHUM) Research Center, [b]Université de Montréal, [c]Internal Medicine, [d]Radiology Department, CHUM, [e]Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, McGill University, [f]Cardiology, CHUM, [g]Medical Clinic Quartier Latin, and [h]Microbiology, CHUM, Montreal, QC, Canada.

Correspondence to Carl Chartrand-Lefebvre, MD, MSc, Radiology Department, CHUM (University of Montreal Medical Center), 1051, Sanguinet Street, Montréal, QC H2X 0C1, Canada.

Tel: +1 514 890 8450; e-mail: carl.chartrand-lefebvre@umontreal.ca

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Introduction

Cardiovascular disease is one of the most important cause of death in people with HIV (PWH) receiving antiretroviral therapy (ART) [1,2]. An increased risk of coronary artery disease (CAD) in this population has been demonstrated in several large cohort studies [3–5]. More recently, studies using coronary computed tomography (CT) angiography (CCTA) have allowed noninvasive characterization of coronary atherosclerosis in PWH [6–9]. Most studies showed a higher prevalence of noncalcified coronary plaques as well as plaques with CT markers of vulnerability (high-risk plaques) in individuals with HIV compared with controls [6–9]. Noncalcified plaques and high-risk plaques have been associated with an increased risk of cardiovascular events [10,11]. Reasons for higher prevalence of high-risk plaques in HIV are still imprecise, although ART [12] and HIV infection itself may be involved.

People with HIV are known to experience changes in body fat distribution characterized by visceral fat accumulation [13,14]. Epicardial fat is the visceral fat of the heart, and ex-vivo and in-vivo studies suggest that this adipose tissue depot may play a unique role in CAD because of its proximity to the coronary arteries. Epicardial fat secretes active mediators in direct vicinity to the coronary arteries that are known to promote inflammation and atherosclerosis [15–18]. Recent studies have shown an association between epicardial fat and the presence and progression of coronary artery disease in the general population [19–22]. In PWH, studies have demonstrated an association between epicardial fat and coronary artery calcium score, noncalcified plaques and adverse cardiovascular events [23–25].

In the present study, we measured epicardial fat in participants living with HIV and controls from a large prospective multicentric cohort, using CCTA. We investigated its association with coronary artery plaque burden, and, more specifically, with coronary plaque volume and low attenuation plaque, a marker of plaque vulnerability. We hypothesized that the volume of epicardial fat will be increased in individuals living with HIV and that it will be associated to coronary artery plaque volume and low attenuation plaque.

Methods

Study design

This is a cross-sectional study nested in the Canadian HIV and Aging Cohort Study (CHACS), an ongoing, multicenter, controlled prospective cohort study following 1000 participants living with HIV and 200 controls in 10 Canadian centers. The full study protocol of CHACS has been described previously [26].

CHACS recruitment is hospital-based as well as community-based, for both individuals with HIV and controls. Participants living with HIV aged 40 years or older, or who have lived with HIV for 15 years or more, were recruited from the HIV clinics of the participating centers from 2012 to 2018. Controls were also aged 40 years or older. They were selected from an outpatient internal medicine clinic, or from the general population.

Study population

Consecutive participants living with HIV and controls with low-to-intermediate cardiovascular risk (10-year Framingham risk score 5–20%) and without symptoms or history of CAD were prospectively invited to undergo noncontrast cardiac CT and coronary CT angiography. Exclusion criteria included creatinine clearance of less than 50 ml/min and history of contrast media allergy.

Data collection

CHACS participants are followed yearly. At each study visit, participants have a complete medical history and physical examination and have a panel of blood tests. Data from the visit closest to the cardiac CT date were obtained (generally within 6–8 months of the scan) including demographics, CAD risk factors and measures of the activity of HIV disease.

Cardiac computed tomography imaging

A 256-slice CT scanner (Brilliance iCT; Philips Healthcare, Best, The Netherlands) was used to perform noncontrast cardiac CT and CCTA.

The following parameters were used for noncontrast CT: slice thickness 2.5 mm, matrix 512 × 512, field-of-view 250 mm, scan voltage 120 kV and prospective ECG gating. Patients were given 50–75 mg of metoprolol orally 45–60 min prior to CCTA if heart rate was greater than 60 bpm, and 0.4 mg of nitroglycerin sublingually, in absence of contraindications. For coronary CCTA, contrast agent was injected at a flow rate of 5 ml/s, using 370 mg/ml of iopamidol (Bracco Imaging, Milan, Italy). Images were reconstructed using a hybrid iterative reconstruction algorithm (Philips iDose, Philips Healthcare, level 3).

Exposure of interest: epicardial fat volume

Epicardial fat volume (cm^3) was quantified using noncontrast cardiac CT images. Epicardial fat was defined as the adipose tissue between the myocardium and the visceral pericardium. Volume was measured by tracing manually the pericardium every two to three slices on axial images from the pulmonary artery bifurcation to the apex of the heart, using a semi-automated software (Aquarius Intuition version 4.4.11; TeraRecon Headquarters, Forster City, California, USA). CT attenuation thresholds between −190 and −30 Hounsfield units (HU) were used to select the epicardial fat and exclude any other tissue. The epicardial fat volumes measured at

each level were then summed to obtain the total epicardial fat volume (Figure 1, Supplemental Data, http://links.lww.com/QAD/C103). Inter-observer and intra-observer agreement for epicardial fat volume measurement was highly reproducible (intraclass correlation coefficient for inter-observer agreement = 0.75 and for intra-observer agreement= 0.97). Image assessors for epicardial fat and coronary plaque were blinded to HIV status and clinical data.

Outcome of interest: coronary plaque volume

Coronary plaque analysis was performed using CCTA images as previously described in Chen *et al.* [27]. The coronary segments were defined as reported in the American College of Cardiology/American Heart Association guidelines for coronary angiography [28]. Plaques were identified and defined as calcified, noncalcified or mixed. Plaque volumetric analysis was performed in multiplanar reformat (MPR), using the aforementioned semi-automated software. First, proximal and distal plaque boundaries were traced by manual segmentation. Then, the software allowed for semiautomatic delimitations between lumen, vessel wall and plaque followed by manual adjustment. Plaque composition was assessed using attenuation-stratified measurements in the plaque volume: 30 HU or less, 31–50, 51–100, 101–150, 151–350 HU and greater than 350 HU.

Total plaque volume per participant was defined as the sum of aforementioned attenuation-stratified measurements. Calcified, noncalcified and mixed plaque volumes per participant were defined as the sum of volumes of calcified, noncalcified and mixed plaques per participant.

Low-attenuation plaque component was defined as 30 HU or less measurements. Low attenuation plaque component portion per participant was determined as the ratio of low attenuation plaque volume and total plaque volume, in each participant with presence of plaque.

Covariates and effect modifiers

Confounders were defined using clinical reasoning as variables likely to be associated with epicardial fat and coronary atherosclerosis. This included traditional cardiovascular risk factors (age, sex, diabetes, high blood pressure, smoking, cholesterol level and statin use), as well as BMI. We also assessed effect modification by HIV status.

Statistical analysis

Continuous data are presented as mean ± standard deviation or median [25th–75th interquartile range (IQR)], as appropriate. Categorical data are presented as numbers and percentages. Differences between participants living with HIV and controls were analysed using Student's *t* test or Mann–Whitney *U* test for normally and nonnormally distributed continuous variables, and chi-squared test for categorical variables, respectively.

Linear regression analyses were performed to evaluate the associations between cardiovascular risk factors, HIV-related parameters and epicardial fat volume in participants living with HIV. The association between ART exposition duration and epicardial fat volume was first assessed altogether, and then specific ART classes were assessed in a separate model to avoid collinearity.

The association of epicardial fat volume and plaque volume variables (total, calcified, noncalcified and mixed) was assessed using zero-inflated Poisson regression. This statistical model is used for continuous distributions with a high prevalence of 'zero' and no overdispersion. It performs both logistic regression to examine factors associated to plaque presence and Poisson regression to evaluate factors associated with plaque volume, each with two separate *P* values, and has been used previously to analyse plaque volume [29]. Coronary plaque volume variables were natural-log transformed prior to statistical analysis.

Association of epicardial fat volume with low attenuation plaque component portion was assessed using linear regression analyses.

All multivariate analyses were performed with adjustment for HIV serostatus, cardiovascular risk factors and BMI, which were included if they showed a univariate association with the outcome with a *P* value 0.1 or less. Effect modification by HIV of each association was assessed by inclusion of an interaction term to the fully adjusted models.

For patients with incomplete continuous covariable data, the mean or median value was used to impute the missing data. Values for the following number of participants were missing and imputed: BMI (5), smoking exposure (14), HDL-cholesterol (4), LDL-cholesterol (9), ART exposition duration (7), nonnucleoside reverse transcriptase inhibitors (NNRTIs) exposition duration (7). A *P* value less than 0.05 was considered statistically significant. Statistical analyses were performed using R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Ethics

This study was approved by the Institutional Review Board of the Medical Center of the University of Montreal (CHUM) and participating centers. All participants gave written informed consent.

Results

Clinical characteristics of participants

A total of 250 consecutive participants were included in the present study. One hundred and sixty-nine (67.6%)

Table 1. Demographic and clinical characteristics of participants, $N = 250$.

Variables	$HIV^+ = 169$	$HIV^- = 81$	*P* value
Age (years)	55.6 ± 7.0	56.6 ± 7.9	0.323
Male sex [*n* (%)]	156 (92.3%)	64 (79.0%)	0.005
Race [*n* (%)]			0.143
Asian	3 (1.8%)	0 (0%)	
Black	15 (8.9%)	2 (2.5%)	
Caucasian	141 (83.4%)	76 (93.8%)	
Hispanic	9 (5.3%)	3 (3.7%)	
10-year Framingham risk score (%)	10 [7–15]	10[7–15]	0.617
Diabetes [*n* (%)]	18 (10.6%)	2 (2.5%)	0.047
High blood pressure [*n* (%)]	53 (31.4%)	20 (24.7%)	0.349
Family history of premature CVD [*n* (%)]	35 (20.7%)	17 (21.0%)	1
Smoking status [*n* (%)]			0.001
Current	53 (31.4%)	9 (11.1%)	
Ex	62 (36.7%)	34 (42.0%)	
Never	51 (30.2%)	37 (47.7%)	
Smoking exposure (pack/year)	6 [0–25.9]	0.1 [0–7.9]	<0.001
Total-cholesterol (mmol/l)	4.9 ± 1.1	5.2 ± 1.0	0.011
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.4 ± 0.4	0.002
LDL-cholesterol (mmol/l)	2.8 ± 0.9	3.2 ± 0.9	0.002
Statin [*n* (%)]	52 (30.8%)	15 (18.5%)	0.058
BMI (kg/m^2)	25.3 ± 4.1	27.1 ± 4.5	0.003
Waist circumference (cm)	95.0 ± 11.6	95.5 ± 11.1	0.751
HIV-specific variables	$HIV^+ = 169$	–	–
HIV infection duration (years)	18.3 ± 7.7	–	–
Participants exposed to ART [*n* (%)]	159 (94.1%)	–	–
ART exposition duration (years)[a]	13.5 ± 6.5	–	–
Participants exposed to PIs [*n* (%)]	128 (75.7%)	–	–
Ritonavir [*n* (%)]	114 (67.4%)		
Lopinavir [*n* (%)]	67 (39.6%)		
Atazanavir [*n* (%)]	66 (39.0%)		
Darunavir [*n* (%)]	55 (32.5%)		
Indinavir [*n* (%)]	49 (30.0%)		
PIs exposition duration (years)[a]	9.5 ± 5.1	–	–
Participants exposed to NRTIs [*n* (%)]	159 (94.1%)	–	–
Lamivudine	136 (80.5%)		
Tenofovir	125 (74.0%)		
Emtricitabine	116 (68.6%)		
Abacavir	105 (62.1%)		
Zidovudine	104 (61.5%)		
Stavudine	71 (42.0%)		
NRTIs exposition duration (years)[a]	12.4 ± 6.1	–	–
Participants exposed to NNRTIs [*n* (%)]	107 (63.3%)	–	–
Efavirenz	74 (43.8%)		
Nevirapine	30 (17.7%)		
Rilpivirine	18 (10.6%)		
Etravirine	15 (8.9%)		
Delavirdine	9 (5.3%)		
NNRTIs exposition duration (years)[a]	4.4 [1.9–7.5]	–	–
Participants exposed to INSTIs [*n* (%)]	78 (46.1%)	–	–
Raltegravir	55 (32.5%)		
Dolutegravir	34 (20.1%)		
Elvitegravir	9 (5.3%)		
INSTIs exposition duration (years)[a]	1.9 [1.0–4.2]	–	–
Undetectable viral load[b] [*n* (%)]	148 (87.6%)	–	–
Viral load among detectable	632 [69.2–25981.2]	–	–
Nadir $CD4^+$ cell count (cells/μl)	200 [100–297]	–	–
Current $CD4^+$ cell count (cells/μl)	585 [414–786.8]	–	–
Current $CD8^+$ cell count (cells/μl)	760 [570–1026]		

Normally distributed variables are expressed as mean ± standard deviation, nonnormally distributed variables are expressed as median [Q1–Q3], categorical variables are expressed using proportion (percentage). *P* values are unadjusted. ART, antiretroviral therapy; CVD, cardiovascular disease; INSTI, integrase strand transfer inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

[a]In patients exposed to therapy.

[b]Defined as viral load 40 copies/ml or less.

participants were living with HIV, and 81 (32.4%) were controls. Figure 2 (Supplemental Data, http://links.lww.com/QAD/C103) shows the flow chart of participants. Participant's characteristics stratified by HIV status are described in Table 1. Participants with HIV had a mean age of 55.6 ± 7.0 years whereas controls had a mean age of

Table 2. Cardiac computed tomography results.

Non contrast cardiac CT ($N=250$)	$HIV^+=169$	$HIV^-=81$	P value
Epicardial fat volume (cm^3)	134.2 ± 49.4	118.6 ± 48.6	0.019
Coronary artery calcium score	14.5 [0–126.0]	8.3 [0–70.5]	0.279
Coronary CT angiography ($N=226$)	$HIV^+=149$	$HIV^-=77$	P value
Total plaque prevalence [*n* (%)]	98 (65.8%)	41 (53.2%)	0.284
Total plaque volume (mm^3)[a]	220.4 [78.2–511.2]	154 [69.6–370]	0.414
Calcified plaque prevalence [*n* (%)]	61 (40.9%)	32 (41.6%)	0.817
Calcified plaque volume (mm^3)[a]	98.4 [50.7–223.1]	111.1 [53.4–256.7]	0.437
Non calcified plaque prevalence [*n* (%)]	31 (20.8%)	6 (7.8%)	0.028
Noncalcified plaque volume (mm^3)[a]	94.4 [31.6–155.9]	31 [15.0–90.9]	0.096
Mixed plaque prevalence [*n* (%)]	70 (47%)	23 (28.9%)	0.035
Mixed plaque volume (mm^3)[a]	137.5 [75.7–341.1]	120 [67.1–286]	0.497
Low attenuation plaque component portion among participants with plaque (%) ($n=139$)	27.4 ± 8.4	27.0 ± 10.9	0.850

Normally distributed variables are expressed as mean ± standard deviation, nonnormally distributed variables are expressed as median [Q1–Q3], categorical variables are expressed using proportion (percentage). *P* values are unadjusted. CT, computed tomography.
[a]In patients with plaque present.

56.6 ± 7.9 years ($P=0.323$). Of participants with HIV, 92.3% were men whereas 79% of controls were men ($P=0.005$).

There was no significant difference in 10-year Framingham risk score between participants living with HIV and controls (median 10[7–15]% in participants living with HIV and 10[7–15]% in controls, $P=0.617$). Participants with HIV were more exposed to smoking than controls (6[0–25.9] in participants with HIV vs. 0.1[0–7.9] pack-years in controls, $P<0.001$). Participants living with HIV had lower total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol (all $P<0.05$), and a higher statin exposure (30.8 vs. 18.5%, $P=0.058$). Participants living with HIV had lower BMI than controls (25.3 ± 4.1 vs 27.1 ± 4.5 kg/m^2, respectively, $P=0.003$).

At time of enrollment, 94.1% of the participants living with HIV had initiated ART with a mean duration of 13.5 ± 6.5 years. Viral load was undetectable (<40 cop-copies/ml) in 87.6%. The median [IQR] $CD4^+$ T-cell count was 585[414–786.8] cells/μl and the median nadir $CD4^+$ T-cell count was 200[100–297] cells/μl.

Cardiac computed tomography results

Cardiac CT results stratified by HIV status are presented in Table 2. All participants had a noncontrast cardiac CT. Of these, 226 (90.4%) participants (149 participants living with HIV and 77 controls) underwent CCTA. Twenty-four did not have CCTA for the following reasons: 4 had a history of contrast allergy, 10 had altered renal function, and 10 refused CCTA. Epicardial fat volume was significantly increased in participants living with HIV (134.2 ± 49.4) compared with controls (118.6 ± 48.6) ($P=0.019$). This difference remained significant even after adjustment for sex, BMI, smoking exposure in pack-year and statin use ($P=0.001$). No difference in coronary calcium score was observed between individuals living with HIV and controls (14.5[0–126.0] and 8.3[0–70.5] respectively, $P=0.279$). Among participants who underwent CCTA, prevalence of noncalcified and mixed plaque was significantly higher in participants living with HIV compared with controls (20.8% in participants with HIV vs. 7.8% in controls, $P=0.028$ for noncalcified plaque and 47% in participants with HIV vs. 28.9% in controls, $P=0.038$ for mixed plaques). However, no difference was observed when comparing total plaque volume and subtypes plaque volume as well as low attenuation plaque percentage among participants with plaques.

Predictors of epicardial fat volume in HIV-infected participants

Table 3 shows the cardiovascular risk factors and HIV-specific parameters associated with epicardial fat volume in the participants living with HIV. In the nonadjusted regression analysis, epicardial fat volume was positively associated with diabetes ($\beta=38.45$, $P=0.002$), smoking exposure ($\beta=0.40$ per additional pack-year, $P=0.041$), statin use ($\beta=9.20$, $P<0.001$), BMI ($\beta=5.66$, $P<0.001$) and NNRTI exposure duration ($\beta=2.73$ per additional year of exposure, $P=0.002$). In addition, there was a trend to a positive association between epicardial fat volume and high blood pressure ($\beta=14.72$, $P=0.072$) and ART exposition duration ($\beta=1.01$ per additional year of exposure, $P=0.083$).

There were inverse association with levels of LDL-cholesterol ($\beta=-8.85$ per increase of 1 mmol/l, $P=0.043$) and HDL-cholesterol ($\beta=-22.73$ per increase of 1 mmol/l, $P=0.033$), and with detectable viral load ($\beta=-37.42$, $P=0.007$).

In multivariate models, only smoking exposure ($\beta=0.34$, $P=0.044$), statin use ($\beta=17.77$, $P=0.015$), BMI ($\beta=5.35$, $P<0.001$), ART exposure duration ($\beta=1.17$, $P=0.026$) and more specifically NNRTI exposure

Table 3. Association of epicardial fat volume with cardiovascular risk factors and HIV-specific parameters in participants living with HIV ($N = 169$).

	Univariate analysis		Multivariate analysis[c]		Multivariate analysis[d]	
	Beta[a] (95% CI)	*P* value	Beta[a] (95% CI)	*P* value	Beta[a] (95% CI)	*P* value
Age (per 1 year increase)	0.46 (−0.62 to 1.55)	0.397	–	–	–	–
Male sex	0.24 (−28.00 to 28.49)	0.986	–	–	–	–
Diabetes	38.45 (14.76–62.13)	0.002	14.11 (−7.06 to 35.29)	0.190	18.80 (−2.18 to 39.78)	0.079
High blood pressure	14.72 (−1.35 to 30.78)	0.072	3.02 (−11.29 to 17.34)	0.677	4.21 (−9.67 to 18.09)	0.550
Smoking exposure (per 1 pack/year increase)	0.40 (0.02–0.78)	0.041	0.34 (0.01–0.67)	0.044	0.37 (0.05–0.70)	0.024
LDL-cholesterol (per 1 mmol/l increase)	−8.85 (−17.43 to −0.28)	0.043	−4.25 (−11.80 to 3.31)	0.268	−4.06 (−11.53 to 3.41)	0.285
HDL-cholesterol (per 1 mmol/l increase)	−22.73 (−43.56 to −1.91)	0.033	−14.89 (−33.10 to 3.30)	0.108	−16.77 (−34.65 to 1.10)	0.066
Statin use	29.20 (13.51–44.89)	<0.001	17.77 (3.44–32.10)	0.015	14.29 (−0.16 to 28.73)	0.052
BMI (per 1 kg/m^2 increase)	5.66 (4.03–7.30)	<0.001	5.35 (3.71–7.00)	<0.001	4.86 (3.29–6.43)	<0.001
HIV infection duration (per 1 year increase)	0.27 (−0.70 to 1.25)	0.579	–	–	–	–
ART exposition duration (per 1 year increase)	1.01 (−0.14 to 2.17)	0.083	1.17 (0.14–2.20)	0.026	–	–
NNRTI exposition duration (per 1 year increase)	2.73 (1.00–4.47)	0.002	–	–	2.19 (0.70–3.68)	0.004
NRTI exposition duration (per 1 year increase)	0.74 (−0.48 to 1.97)	0.231	–	–	–	–
PI exposition duration (per 1 year increase)	−0.59 (−1.89 to 0.70)	0.367	–	–	–	–
INSTI exposition duration (per 1 year increase)	0.15 (−3.68 to 3.98)	0.939	–	–	–	–
Nadir CD4$^+$ cell count (per 100 cells/μl)	2.96 (−2.33 to 8.24)	0.271	–	–	–	–
Current CD4$^+$ cell count (per 100 cells/μl)	0.90 (−1.54 to 3.34)	0.468	–	–	–	–
Current CD8$^+$ cell count (per 100 cells/μl)	0.30 (−1.60 to 2.20)	0.752	–	–	–	–
Detectable viral load[b]	−37.42 (−64.38 to −10.46)	0.007	−16.15 (−39.58 to 7.28)	0.175	−18.78 (−41.57 to 4.01)	0.105

Multivariate analyses included cardiovascular risk factors and HIV-related parameters if they showed an association with the outcome in the univariable model with a *P* value 0.1 or less. ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.
[a]Beta can be interpreted as the mean increase in epicardial fat volume (in cm^3) predicted by the model per each one unit change in the explanatory variable. A negative beta coefficient indicates a decrease.
[b]Defined as viral load greater than 40 copies/ml (0: no detectable viral load, 1: detectable viral load).
[c]Adjusted for cardiovascular risk factors including diabetes, high blood pressure, smoking, LDL-cholesterol, HDL-cholesterol, statin use, BMI, ART exposition duration and undetectable viral load.
[d]Adjusted for cardiovascular risk factors including diabetes, high blood pressure, smoking, LDL-cholesterol, HDL-cholesterol, statin, BMI, NNRTI exposition duration and undetectable viral load.

Table 4. Association of epicardial fat volume with total coronary plaque and specific subtypes of plaque, using coronary computed tomography angiography, $N = 226$.

	All participants with coronary CT angiography ($N = 226$)[a]					
	Univariate analysis			Multivariate analysis		
	Regression	Estimate (95% CI)	*P* value	Regression	Estimate (95% CI)	*P* value
Total plaque volume[b] (per 10 cm^3 increase)						
$V = 0$: 77	Logistic	1.02 (0.96 – 1.07)	0.553	Logistic	0.97 (0.90–1.05)	0.496
$V > 0$: 139	Poisson	1.01 (1.00–1.03)	0.087	Poisson	1.01 (0.99–1.02)	0.494
Noncalcified plaque volume[c] (per 10 cm^3 increase)						
$V = 0$: 178	Logistic	1.07 (1.00–1.13)	0.061	Logistic	1.09 (1.01–1.18)	0.028
$V > 0$: 37	Poisson	1.00 (0.97 – 1.03)	0.949	Poisson	0.99 (0.95–1.03)	0.696
Calcified plaque volume[d] (per 10 cm^3 increase)						
$V = 0$: 122	Logistic	1.01 (0.95–1.06)	0.821	Logistic	0.93 (0.85–1.00)	0.060
$V > 0$: 93	Poisson	1.01 (0.99–1.03)	0.222	Poisson	1.00 (0.98–1.03)	0.753
Mixed plaque volume[e] (per 10 cm^3 increase)						
$V = 0$: 122	Logistic	1.03 (0.97–1.08)	0.348	Logistic	0.99 (0.99–1.03)	0.292
$V > 0$: 93	Poisson	1.01 (0.99–1.01)	0.265	Poisson	1.00 (0.89–1.01)	0.279

Multivariate analyses were adjusted for HIV status and BMI. Adjustment also included cardiovascular risk factors when these showed an association with the outcome in the univariable model with a *P* value 0.1 or less.
[a]Two hundred and twenty-six participants with plaque volume and epicardial fat volume assessment with CT; plaque volume measurements were missing in 10 of these participants. $V = 0$: Plaque volume = 0 mm^3, with number of participants with plaque volume of zero; *V* greater than 0: plaque volume greater than 0 mm^3, with number of participants with plaque volume more than 0 mm^3.
[b]Adjusted for HIV status, BMI, age, smoking exposure and statin use.
[c]Adjusted for HIV status, BMI and statin use.
[d]Adjusted for HIV status, BMI, age, smoking exposure, LDL-cholesterol and statin use.
[e]Adjusted for HIV status, BMI, age, smoking exposure and statin use.

duration ($\beta = 2.19$, $P = 0.004$) remained significantly associated with epicardial fat volume.

Epicardial fat volume and coronary plaque

Nonadjusted and adjusted associations of epicardial fat volume and coronary plaque including total volume of plaques and volume of calcified, noncalcified and mixed plaque subtypes are presented in Table 4. After adjustment for HIV status, BMI and traditional cardiovascular risk factors, there was no significant association between epicardial fat volume and total plaque volume [odds ratio (OR) for logistic regression = 0.97 (0.90–1.05) per 10 cm^3 increase in epicardial fat, $P = 0.496$ and OR for Poisson regression = 1.01 (0.99–1.02) per 10 cm^3 increase in epicardial fat, $P = 0.494$]. However, after stratification of plaque volume according to plaque subtypes, a significant association between epicardial fat volume and noncalcified plaque volume was observed (OR for logistic regression =1.09 (1.01–1.18) per 10 cm^3 increase in epicardial fat, $P = 0.028$ and OR for Poisson regression = 0.99 (0.95–1.03) per 10 cm^3 increase in epicardial fat, $P = 0.696$) whereas no association was observed with calcified or mixed plaque volumes. There was no evidence of interaction by HIV status in these analyses.

Table 5 presents linear regression analysis assessing the relationship between epicardial fat volume and low attenuation coronary plaque component portion among 139 participants with at least one plaque (98 participants living with HIV and 41 controls). In univariate regression analysis, epicardial fat volume ($\beta = 0.62$ per 10 cm^3 increase, $P < 0.001$), HDL-cholesterol ($\beta = -4.99$, $P = 0.038$), statin use ($\beta = 3.84$, $P = 0.020$) and BMI ($\beta = 0.53$, $P = 0.001$) were all associated with low attenuation coronary plaque. After multivariate analysis, only epicardial fat volume remained significantly associated to low attenuation plaque component portion ($\beta =$ 0.38 per 10 cm^3 increase in epicardial fat, $P = 0.026$). There was no evidence of interaction by HIV status in these analyses.

Discussion

Our study involves 250 consecutive participants living with HIV and noninfected controls that underwent prospective CT assessment of epicardial fat volume and subclinical coronary plaque burden, nested in a prospective multicentric cohort. All participants were well characterized, asymptomatic and with mild-to-moderate cardiovascular calculated risk. We found that epicardial fat volume was significantly increased in participants living with HIV compared with controls. Among participants with HIV, duration of exposure to ART, especially NNRTI, was associated with increased epicardial fat, whereas no association was found with other markers of HIV infection. Finally, we showed that epicardial fat volume is associated to noncalcified coronary plaque volume and low attenuation plaque component portion, which is a marker of plaque vulnerability, independently of traditional cardiovascular risk factors.

Table 5. Association of epicardial fat volume with low attenuation coronary plaque component portion in participants with at least one plaque, $N = 139$ (98 HIV^+ and 41 HIV^-).

	All participants ($N = 139$)			
	Univariate analysis		Multivariate analysis	
	Beta (95% CI)	*P* value	Beta (95% CI)	*P* value
Epicardial fat volume (per 10 cm^3 increase)	0.62 (0.36–0.89)	<0.001	0.38 (0.05–0.72)	0.026
Age (per 1 year increase)	−0.06 (−0.26 to 0.14)	0.549	–	–
Sex (men vs. women)	0.52 (−4.30 to 5.34)	0.832	–	–
HIV (no vs. yes)	0.36 (−3.01 to 3.73)	0.834	−0.62 (−4.08 to 2.84)	0.724
Diabetes (no vs. yes)	5.38 (−0.02 to 10.78)	0.051	2.64 (−2.76 to 8.04)	0.336
High blood pressure (no vs. yes)	1.46 (−1.81 to 4.74)	0.379	–	–
Smoking exposure (per 1 pack/year increase)	0.02 (−0.06 to 0.10)	0.677	–	–
LDL-cholesterol (per 1 mmol/l increase)	−1.31 (−2.90 to 0.28)	0.106	–	–
HDL-cholesterol (per 1 mmol/l increase)	−4.99 (−9.70 to −0.28)	0.038	−3.14 (−7.88 to 1.59)	0.191
Statin use (no vs. yes)	3.84 (0.62–7.06)	0.020	2.41 (−0.87 to 5.68)	0.149
BMI (per 1 kg/m^2 increase)	0.53 (0.21–0.86)	0.001	0.25 (−0.12 to 0.63)	0.187

Multivariate analyses included cardiovascular risk factors if they showed an association with the outcome in the univariable model with a *P* value 0.1 or less. Beta can be interpreted as the mean increase in low attenuation plaque component portion (in %) predicted by the model per each one unit change in the explanatory variable. A negative beta coefficient indicates a decrease.

People with HIV experience changes in body fat distribution, known as lipodystrophy, characterized by greater visceral fat and/or less subcutaneous fat [13,14,30]. Studies that compared epicardial fat volume in PWH and noninfected controls have shown mixed results. Studies described epicardial fat volume as increased among HIV-infected participants [25,31–33], whereas such a difference has not been demonstrated by others [34–36]. Differences in study samples and populations may explain these results. Of note, the three studies showing no inter-group difference had smaller samples than our study [34–36]. In our study, we prospectively included 250 male and female participants living with HIV and controls with similar cardiovascular risk and demonstrated an increased epicardial fat volume in the HIV group and this remained even after adjusting for confounding factors. This finding supports the hypothesis that individuals living with HIV exposed to long-term ART may present unique characteristics beyond traditional risk factors that contribute to ectopic fat accumulation through specific pathways. These pathways may involve the virus itself and its consequences such as the chronic systemic inflammation and immune activation and/or ART.

Since the introduction of highly active ART, several studies have shown that drugs used in these regimens favor the development of metabolic changes including dyslipidemia [37], glucose level impairment [38] and body fat changes [13]. Despite improvement of newer generations of therapeutic agents, these complications still exist [39]. In our study, we found a positive association between epicardial fat volume and exposure to ART, and more specifically to NNRTIs. Although there have been reports of increased epicardial fat with exposure to NRTIs [25,34,40], and protease inhibitors [41], this finding related to NNRTIs is novel. It should be noted, however, that combinations of ARTs were used in our participants, and therefore, we cannot exclude that the increase of epicardial fat associated to NNRTI may result from a combination effect of NNRTI with other classes, in particular the NRTIs. In addition, most of our participants living with HIV were on ART, and ART duration is correlated to HIV infection duration. HIV infection itself may cause an alteration in the distribution of fat that could be because of direct viral effect, and other underlying immune processes [13,14,42]. Therefore, we are not able to distinguish the effects of HIV-infection from ART in our analyses.

Finally, we found that epicardial fat volume is associated to specific CT features of coronary artery plaque. It has been previously shown that epicardial fat in individuals living with HIV correlates to coronary calcium score [40], plaque prevalence [25] and to an increased risk of adverse cardiovascular events [23]. Using CCTA, Brener *et al.* [25] and Srinivasa *et al.* [34] showed that epicardial fat volume is associated to noncalcified coronary plaques in HIV patients. Our study adds to the current knowledge by demonstrating an independent relationship between epicardial fat volume and noncalcified plaque volume. Furthermore, we present novel data in a study that includes PWH showing an association between low attenuation plaque, a marker of plaque vulnerability, and epicardial fat volume that appears to be independent of other factors known to be associated to coronary atherosclerosis. CT features, such as low attenuation plaque have been proven to be associated to an increased risk of acute coronary syndromes [10,11,43]. This finding is of particular interest, as studies using CCTA showed that patients living with HIV harbor more high-risk plaque features [7,8]. Epicardial fat that envelops the coronary arteries may exert changes in the artery wall via secretion of cytokines that promotes inflammation and vulnerable atherosclerotic depots [17,18,44]. We may, thus, hypothesize that epicardial fat could be a driver of increased plaque

vulnerability in HIV. Furthermore, we could hypothesize that epicardial fat imaging using CT could eventually be used as a screening tool for high-risk plaque, although this will need further studies with a methodology specifically designed to address this question.

Strengths of our study are worth being noted: we studied a group of individuals living with HIV and controls, men and women. Our data demonstrates for the first time that epicardial fat, volumetrically assessed with cardiac CT, is related to a high-risk plaque feature. We measured epicardial fat on noncontrast cardiac CT images obtained generally for the purpose of measuring coronary calcium score, requiring no supplemental radiation exposure for the evaluation of epicardial fat. In addition, we measured the full epicardial fat volume, which is a more reproducible and superior measure than epicardial fat thickness.

Our study has some limitations. This was a cross-sectional analysis and as such, no cause and effect can be inferred from the associations found. Additionally, as a small group of participants had calcified, noncalcified or mixed plaques, the analyses on plaque sub-types may have lacked statistical power. This was also true for antiretroviral therapy, where a small group of participants were in each sub-class of ART. Some of our participants were on integrase inhibitors (INSTI), and notably, there is mounting evidence that this class is associated with more weight gain [45,46]. Future studies should investigate the association of INSTI with epicardial fat. Our study was conducted in participants who were predominantly male. It remains unknown whether these findings can be generalized to women. Finally, the exclusion of participants with renal failure could have underestimated CAD. Although this does not bias our results, it limits their generalizability to populations with renal failure.

In conclusion, our study demonstrates that epicardial fat volume is increased in individuals living with HIV. It is associated to ART exposure duration, especially NNRTIs, to noncalcified coronary plaque volume, as well as to the low attenuation component of the plaque, a known marker of plaque vulnerability. These results suggest a potential pathway by which epicardial fat could be a silent driver of subclinical coronary artery disease in the HIV population. These data may steer future studies to investigate further the increased cardiovascular risk in PWH.

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Conflicts of interest

There are no conflicts of interest.

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