Higher epicardial fat in older adults living with HIV with viral suppression and relationship with liver steatosis, coronary calcium and cardiometabolic risks

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Objectives: HIV infection is associated with ectopic fat deposition, which leads to chronic inflammation and cardiometabolic dysregulation. We assessed the epicardial adipose tissue (EAT) volume and its associated factors among people with HIV (PWH).

Design: A cross-sectional study.

Methods: We conducted a cross-sectional study among PWH aged at least 50 years and age-matched and sex-matched HIV-negative older individuals in Bangkok, Thailand. Participants underwent a noncontrast, cardiac computed tomography (CT) scan to assess coronary artery calcium (CAC) score and EAT between March 2016 and June 2017. Multivariate linear regression analyses were used to investigate HIV-related factors, cardiac and metabolic markers associated with EAT volume.

Results: Median age was 55 years [interquartile range (IQR) 52–60] and 63% were men. Median duration of antiretroviral therapy (ART) was 16 years with 97% had HIV-1 RNA less than 50 copies/ml and median $CD4^+$ cell count of 617 cells/μl. Median EAT volume was significantly higher in PWH [99 (IQR 75–122) cm^3] than HIV-negative individuals [93 (IQR 69–117) cm^3], $P = 0.022$. In adjusted model, factors associated with EAT volume included male sex ($P = 0.045$), older age ($P < 0.001$), abnormal waist circumference ($P < 0.001$) and HOMA-IR ($P = 0.01$). In addition, higher CAC score was independently associated with EAT volume. Higher mean EAT volume was seen in PWH with severe liver steatosis than those without steatosis ($P = 0.018$). In adjusted PWH-only model, duration of HIV was significantly associated with higher EAT volume ($P = 0.028$).

Conclusion: In an aging cohort, PWH had higher EAT volume than HIV-negative controls. EAT was also independently associated with central fat accumulation, insulin resistance, liver steatosis and CAC score.

AIDS 2022, **36**:1073–1081

Keywords: cardiovascular disease, epicardial fat volume, HIV, insulin resistance, liver steatosis

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Received: 13 November 2021; revised: 28 January 2022; accepted: 17 February 2022.

DOI:10.1097/QAD.0000000000003204

Introduction

People with HIV (PWH) have near-normal life expectancy as individuals without HIV infection with the advances of antiretroviral therapy (ART) [1,2]. HIV infection is characterized by persistent inflammation and chronic immune activation, which are associated with multiple cardiometabolic complications [3,4]. Ectopic visceral fat deposition is commonly seen among PWH treated with antiretroviral therapy [5]. Epicardial adipose tissue (EAT) is located within the pericardial sac that surrounds the heart and it has the same arterial supply as the coronary arteries [6]. EAT has been shown to influence myocardial function and to be associated with atherosclerotic cardiovascular diseases [7]. Previous studies in HIV-negative population have suggested EAT was associated with cardiovascular risk factors including metabolic syndrome, insulin resistance [8] and sub-clinical coronary atherosclerosis markers, such as coronary calcium and plaque formation [9,10]. Moreover, recent studies have also described the associations of EAT volume with liver fibrosis and nonalcoholic fatty liver diseases [11,12], as epicardial fat and visceral fat share the same embryonic origin: brown fat [13].

A few studies have also described the association of EAT with metabolic parameters, immune activation and systemic inflammation in PWH population [14,15]. However, little is known regarding the EAT among elderly PWH who are on suppressive ART. Therefore, in this study, we investigated the EAT using cardiac computed tomography (CT) scans among PWH older than 50 years treated with a median of 16 years of ART, matched with HIV-negative individuals, and explored the factors associated with EAT volume, including liver-related parameters, such as liver fibrosis and steatosis.

Methods

Study population and design

A cross-sectional study was conducted among persons with HIV aged at least 50 years in a HIV cohort (HIV-NAT 006: clinical trial number NCT00411983) at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Centre in Bangkok, Thailand from March 2016 to June 2017. HIV-negative participants were included by matching with age and sex to persons with HIV. HIV-negative participants were recruited from individuals aged at least 50 years attending an outpatient general clinic of the King Chulalongkorn Memorial Hospital (KCMH) in Bangkok, Thailand during the same period. The eligibility criteria were applied similarly for both PWH and HIV-negative controls. All participants underwent noncontrast cardiac CT scan for the evaluation of coronary artery calcium score (CAC) and epicardial fat volume at KCMH, Bangkok, Thailand.

Eligibility

Participants with known underlying cardiovascular diseases, such as myocardial infarction, ischemic heart diseases, myocardial ischemia, strokes and those who have previously underwent coronary interventions/procedures including coronary artery surgery and angioplasty were excluded. Persons with abnormal fat distribution, such as Cushing syndrome, hypercortisolism and those who have been exposed to exogenous steroid use were excluded. Of note, the clinical status of abnormal fat distribution was made by the physician's diagnosis, which was based on physical examinations and patient's history. Participants with active opportunistic infections or immunocompromised conditions, such as those receiving chemotherapy were also excluded.

Ethical consideration

Written informed consents were obtained from all participants for the participation of the study with all research performed in accordance to the relevant clinical practices and guidelines. This study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

Noncontrast cardiac computed tomography scans, and measurement of epicardial adipose tissue

The noncontrast cardiac CT scans were performed in both HIV-positive and HIV-negative participants at King Chulalongkorn Memorial Hospital using Dual-Source CT scanner (SOMATOM Force, Siemens, Germany). The standard parameters included prospective ECG-triggering, 3 mm slice thickness, 1.2×48 mm collimation, and 0.25 s rotation at 120 kVp. The EAT was measured by one experienced radiologist who was blinded from patient care. Using the semi-automated technique, Synapse 3D software (FujiFilm Medical, Tokyo, Japan), the region of interest (ROI) was traced along the outline of pericardium in every 3 mm thickness axial slice of the heart manually. The upper and lower heart boundaries were measured from one slice above left main coronary artery down to the last slice containing any portion of heart. In order to get the epicardial fat volume, the CT attenuation threshold was set between -200 to -30 Hounsfield unit (HU) to quantify fat tissue within pericardium [16,17].

Study outcomes, demographic, and other clinical parameters

The primary outcomes of the study were to investigate the EAT volume (presented in cm^3) in all participants, regardless of HIV status and to compare the differences in EAT volume by covariates. The secondary outcome was to explore the factors associated with EAT volume in all participants and in HIV-positive participants.

The collected demographic and clinical information included age, sex, HIV status, BMI, waist circumferences, fasting blood glucose and lipid profiles, insulin levels,

medical history, such as diabetes mellitus and hypertension, smoking status (never, current and ever), current statin use and hepatitis B and C (HBV, HCV) co-infection. HBV and HCV infection was defined as positive surface antigen and antibody, respectively. Diabetes mellitus was defined as fasting blood glucose at least 126 mg/dl for two consecutive visits, use of antidiabetic treatment, and reported onset of diabetes. Hypertension was defined as SBP at least 140 mmHg or DBP at least 90 mmHg on two or more clinic visits and/or initiation of antihypertensive agents. Abnormal waist circumference was defined as waist circumference greater than 90 cm in men or greater than 80 cm in women. Controlled attenuation parameter (CAP) and liver fibrosis measurements for assessing liver steatosis and fibrosis were also obtained from transient elastography (FibroScan, Echosens, Paris, France), which were performed within 1-week window period of cardiac CT scans. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated using the formula: fasting insulin (μU/l) $\times$ fasting glucose (nmol/l)/22.5 [18]. The quantification of the CAC score was used by the Agatston method [19].

HIV-related parameters, such as nadir and current $CD4^+$ cell count, HIV-1 RNA level, duration of HIV and ART, types of ART regimen [nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor), and duration of stavudine (D4T) and abacavir (ABC) use were also included.

Statistical analysis

HIV-negative individuals were frequency matched to HIV-positive participants by sex and age in 5-year intervals. Continuous variables are presented in mean ($\pm$SD, standard deviation) or median [interquartile range (IQR)], and categorical variables are presented as number and percentage. Comparisons were made between HIV-positive and HIV-negative individuals by using Student's *t* tests or Wilcoxon rank-sum tests as appropriate for continuous variables, and a chi-square or Fisher's exact test for categorical variables. Spearman rank correlation coefficients (ρ) were reported for the correlation of variables with EAT volume. Univariable and multivariable linear regression models were used to investigate the traditional factors associated with EAT volume among all participants and HIV-related parameters among PWH. Separate linear regression models were also used to investigate the association of 'log-transformed' EAT volume with CAC, liver stiffness and controlled attenuation parameter (CAP) by FibroScan. Severe liver steatosis was defined as CAP value at least 288 dB/m. Interaction terms included in various models were mentioned in the footnotes under Table 1. Covariates with a *P* less than 0.15 in univariate analysis were included in the multivariable model. A two-tailed *P* value less than 0.05 was considered as statistically significant. All analyses were performed using Stata 16 (StataCorp, College Station, Texas, USA).

Table 1. Relationship of epicardial adipose tissue volume with coronary artery calcium score, liver stiffness and steatosis.

	Univariate		Model 1		Model 2		Model 3		Model 4	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
CAC (>100 vs. <100)	0.06 (0.02–0.1)	**0.005**	0.05 (0.004–0.1)	**0.033**	0.4 (0.1–0.7)	**0.009**	0.49 (0.02–0.97)	**0.042**	0.43 (0.13–0.74)	**0.006**
Liver stiffness (kPa)		0.729								
<7.1	Ref									
7.1–9.5	0.02 (−0.03 to 0.07)	0.395								
9.5–12.5	0.02 (−0.04 to 0.09)	0.442								
>12.5	0.02 (−0.06 to 0.09)	0.663								
CAP (per 50 dB/m increase)	0.03 (0.01 to 0.04)	**<0.001**	0.03 (0.01–0.04)	<0.001	0.01 (−0.01 to 0.02)	0.222	0.01 (−0.01 to 0.02)	0.445	0.01 (−0.01 to 0.02)	0.31

Multivariable linear regression models: model 1 was adjusted for age, sex, HIV status; model 2 was adjusted for model 1 + BMI##sex, BMI##CAC or BMI##CAP; model 3 was adjusted for model 1 + waist circumference##sex, waist circumference##CAC or waist circumference##CAP; model 4 was adjusted for model 2 + triglycerides, statin use, diabetes mellitus, and hypertension. Coefficients can be interpreted as mean difference in $\log_{10}$ epicardial adipose tissue (EAT) volume (cm^3). Positive values indicate increases and negative values indicate decreases in EAT volume in exploratory variable. Bold values represent significant *P*-values. CAC, coronary artery calcium; CAP, controlled attenuation parameter.

Results

A total of 339 HIV-positive and 144 HIV-negative participants underwent cardiac CT scans for the evaluation of EAT volume. There were no significant cardiac/coronary and cerebrovascular events reported from the included participants. Demographic and clinical characteristics of participants are shown in Table 2. The median age was 55 (IQR, 52–60) years and 63% were men. HIV-negative individuals had higher BMI (25.1 vs. 23.1 kg/m^2,

Table 2. Clinical and demographic characteristics of participants.

	Total ($N = 483$)	HIV negative ($N = 144$)	HIV positive ($N = 339$)	P value
Sex				0.831
Female	181 (37.5%)	55 (38.2%)	126 (37.2%)	
Male	302 (62.5%)	89 (61.8%)	213 (62.8%)	
Age (years)	55 (52–60)	58 (54–62)	54 (52–59)	<0.001
Employment				0.832
Unemployed	90 (18.6%)	26 (18.1%)	64 (18.9%)	
Employed	393 (81.4%)	118 (81.9%)	275 (81.1%)	
Monthly income (Thai baht)				0.078
No income	50 (10.4%)	16 (11.1%)	34 (10.0%)	
<10 000	135 (27.9%)	34 (23.6%)	101 (29.8%)	
10 000–19 999	145 (30.0%)	37 (25.7%)	108 (31.9%)	
≥20 000	153 (31.7%)	57 (39.6%)	96 (28.3%)	
Education				<0.001
No education	5 (1.0%)	0 (0%)	5 (1.5%)	
Primary and secondary	218 (45.1%)	86 (59.7%)	132 (38.9%)	
High school and vocational school	129 (26.7%)	27 (18.8%)	102 (30.1%)	
Bachelor's degree or higher	131 (27.1%)	31 (21.5%)	100 (29.5%)	
BMI (kg/m^2)	23.5 (21.2–26.1)	25.1 (22.2–27.6)	23.1 (20.8–25.2)	<0.001
HOMA-IR	1.50 (0.99–2.54)	1.22 (0.83–1.79)	1.64 (1.03–2.74)	0.0003
Diabetes mellitus	82 (17.0%)	21 (14.6%)	61 (18.0%)	0.361
Hypertension	189 (39.1%)	47 (32.6%)	142 (41.9%)	0.057
Waist circumference (cm)	85 (79–91)	87 (80–92)	84 (78–90)	0.010
Total cholesterol (mg/dl)	211 (183–242)	220 (195–248)	203 (178–238)	0.0006
Triglyceride (mg/dl)	143 (99–202)	123 (97–156)	160 (103–221)	<0.001
HDL cholesterol (mg/dl)	48 (40–57)	51 (45–60)	46 (39–57)	<0.001
LDL cholesterol (mg/dl)	128 (103–153)	139 (116–167)	123 (99–147)	<0.001
Smoking status				0.553
Never	308 (63.8%)	93 (64.6%)	215 (63.4%)	
Current smoker	62 (12.8%)	15 (10.4%)	47 (13.9%)	
Ex-smoker	113 (23.4%)	36 (25.0%)	77 (22.7%)	
Coronary calcium score severity				0.72
0	260 (53.8%)	76 (52.8%)	184 (54.3%)	
1–99	145 (30.0%)	45 (31.3%)	100 (29.5%)	
100–399	47 (9.7%)	16 (11.1%)	31 (9.1%)	
≥400	31 (6.4%)	7 (4.9%)	24 (7.1%)	
Hepatitis B co-infection	51/481 (10.6%)	8/142 (5.6%)	43/339 (12.7%)	0.022
Hepatitis C co-infection	34/481 (7.1%)	3/142 (2.1%)	31/339 (9.1%)	0.005
Liver stiffness (kPa)	5.4 (4.4–6.9)	5.4 (4.4–6.8)	5.4 (4.4–7.0)	0.742
CAP score (dB/min)	232 (191–264)	227 (195–255)	232 (191–265)	0.775
Current statin use				0.006
No exposure	330 (68.3%)	114 (79.2%)	216 (63.7%)	
3–6 months	13 (2.7%)	1 (0.7%)	12 (3.5%)	
6–12 months	24 (5.0%)	4 (2.8%)	20 (5.9%)	
≥12 months	116 (24.0%)	25 (17.4%)	91 (26.8%)	
HIV mode of acquisition				
Heterosexual			255 (75.2%)	
MSM			43 (12.7%)	
Blood transfusion			1 (0.3%)	
Injection drug use			2 (0.6%)	
Unknown			35 (10.3%)	
Nadir CD4$^+$ cell cell count (cells/μl)	NA	NA	177 (91–257)	
Current CD4$^+$ cell cell count (cells/μl)	NA	NA	617 (480–797)	
Current CD4$^+$/CD8$^+$ ratio	NA	NA	0.97 (0.69–1.27)	
Current HIV RNA ≤50 copies/ml	NA	NA	331 (97.64%)	
Duration of HIV infection (years)	NA	NA	19 (15–21)	
Duration of ART (years)	NA	NA	16.2 (12.8–19.1)	
Current ART regimen [N (%)]	NA	NA		
NNRTI			185 (54.57%)	
PI			109 (32.15%)	
Others			45 (13.27%)	

CAP, controlled attenuation parameter; CT, computed tomography; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

$P < 0.001$) and waist circumference (87 vs. 84 cm, $P = 0.01$) compared with PWH. There was no difference in cardiovascular risk factors, such as diabetes mellitus ($P = 0.36$) and hypertension ($P = 0.06$) between two groups. Thirteen percent were current smokers. Twenty-five (17%) HIV-negative and 91 (27%) PWH participants were on statin treatment for at least 12 months at the cardiac CT screening date. Majority of them were on atrovastatin (62%) followed by simvastatin (35%), rosuvastatin (2%) and pitavastatin (<1%).

All HIV-positive participants were treated with ART for a median of 16.2 (IQR 12.8–19.1) years. Majority of them were on NNRTI-based regimen, and 32.2% were on protease inhibitors-based regimen at the time of EAT volume evaluation. The median nadir and current $CD4^+$ cell counts were 177 (IQR 91–257) and 617 (IQR 480–797) cells/μl, respectively. The median current $CD4^+/CD8^+$ ratio was 0.97 (IQR 0.69–1.27), and 98% had HIV-1 RNA less than 50 copies/ml.

Epicardial adipose tissue volume measurements

The overall median EAT volume was 97 (IQR 74–120) cm^2, and PWH had higher EAT volume than HIV-negative participants (99 [IQR 75–122], vs. 93 [IQR 69–117] cm^3, $P = 0.02$) (Fig. 1). Overall EAT volume was positively correlated with age ($\rho = 0.221$, $P < 0.001$), BMI ($\rho = 0.350$, $P < 0.001$), HOMA-IR ($\rho = 0.160$, $P = 0.001$), triglycerides (0.180, $P < 0.001$) and waist circumference ($\rho = 0.428$, $P < 0.001$) (Supplementary Table S1, http://links.lww.com/QAD/C465). EAT volume did not differ significantly with nadir or current $CD4^+$ cell count, current $CD4^+/CD8^+$ ratio and types of ART regimen. EAT volume was also differed based on liver steatosis and HOMA-IR (Supplementary Figure S1, http://links.lww.com/QAD/C465). Supplementary Figure S2, http://links.lww.com/QAD/C465 also shows the positive correlation of EAT volume with HOMA-IR ($P < 0.001$).

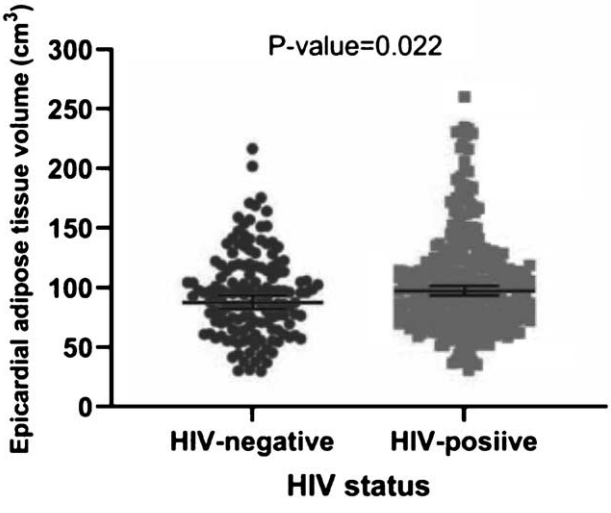

Fig. 1. Epicardial adipose tissue volume (cm^3) by HIV serostatus.

Relationships of epicardial adipose tissue volume with clinical parameters among all participants ($N = 483$)

In univariable model (Table 3), traditional risk factors including age, sex, BMI, HOMA-IR, hypertension, triglycerides, abnormal waist circumference, smoking, current statin use, CAC score and HIV infection were associated with EAT volume. Multivariable regression showed that log-transformed EAT volume was associated with male sex [coefficient = 0.08, 95% confidence interval (CI) 0.01–0.16; $P = 0.045$ vs. female], age per 1 year increase (coefficient = 0.01, 95% CI 0.01–0.02; $P < 0.001$), HOMA-IR at least 2 (coefficient = 0.10, 95% CI 0.02–0.17; $P = 0.10$) compared with HOMA less than 2, abnormal waist circumference (coefficient = 0.27, 95% CI 0.20–0.34, $P < 0.001$), abnormal triglyceride level (coefficient = 0.12, 95% CI 0.05–0.19, $P = 0.001$) and HIV infection (coefficient = 0.11, 95% CI 0.03–0.19; $P = 0.005$).

Relationships of epicardial adipose tissue volume with HIV parameters among HIV-positive participants ($N = 339$)

In the adjusted PWH-only model, only duration of HIV (coefficient = 0.10, 95% CI 0.01–0.19; $P = 0.028$) was associated with EAT volume (Table 4) after adjusting for sex, age, HOMA-IR, abnormal waist circumference, abnormal triglyceride level, smoking, hypertension, diabetes mellitus and lipodystrophy. Other HIV-related parameters, such as nadir $CD4^+$ cell count, types of ART, duration of antiretrovirals, such as stavudine and abacavir use were not evident to be statistically associated with EAT volume in the bivariable models.

Relationships of epicardial adipose tissue volume with coronary artery calcium, liver fibrosis and steatosis

Among all participants, 16 and 6% had CAC score greater than 100 and greater than 400, respectively. The liver stiffness and CAP value from FibroScan was 5.4 (IQR 4.4–6.9) kPa and 232 (IQR 191–264) dB/m, respectively. There were no significant differences in liver stiffness and CAP between the groups of HIV-positive and HIV-negative participants. However, mean EAT volume was significantly higher in participants with severe liver steatosis than those without steatosis in PWH (113.6 ± 41.8 vs. 102.1 ± 40.6 cm^3, $P = 0.018$) but not in HIV-negative individuals ($P = 0.913$) (Supplementary Figure S2, http://links.lww.com/QAD/C465).

EAT volume was significantly associated with CAP ($P < 0.001$) score after adjusting for age, sex, and HIV serostatus (model 1). However, after adjusting BMI (model 2), waist circumference (model 3) or CVD risk factors (model 4), CAP was not evident to be statistically

Table 3. Multivariable linear regression analysis on log-transformed epicardial adipose tissue volume in all participants (*N* = 483).

	Univariate analysis			Multivariable analysis		
Variables	Coefficient	95% CI	*P* value	Coefficient	95% CI	*P* value
Male (vs. female)	0.03	−0.04 to 0.10	0.456	0.08	0.01–0.16	**0.045**
Age (per 1 year increase)	0.01	0.01–0.02	<0.001	0.01	0.01–0.02	**<0.001**
HOMA-IR (≥2 vs. <2)	0.21	0.13–0.28	<0.001	0.10	0.02–0.17	**0.010**
Diabetes mellitus (yes vs. no)	0.15	0.05–0.24	0.002	−0.02	−0.11 to 0.07	0.667
Hypertension (yes vs. no)	0.19	0.12–0.26	<0.001	0.05	−0.02 to 0.07	0.158
Abnormal waist circumference[a] (yes vs. no)	0.28	0.22–0.35	<0.001	0.27	0.20–0.34	**<0.001**
Abnormal triglyceride ≥150 mg/dl (yes vs. no)	0.22	0.16–0.29	<0.001	0.12	0.05–0.19	**0.001**
Abnormal LDL ≥130 mg/dl (yes vs. no)	−0.04	−0.11 to 0.03	0.294			
Smoking status (ever smoke vs. never smoke)	0.05	−0.03 to 0.12	0.220	0.03	−0.05 to 0.10	0.512
Current statin use (yes vs. no)	0.16	0.09–0.24	<0.001	0.06	−0.01 to 0.13	0.106
HCV co-infection[b] (yes vs. no)	−0.07	−0.20 to 0.07	0.318			
HIV positive (vs. negative)	0.11	0.03–0.18	0.006	0.11	0.03–0.19	**0.005**

Coefficients can be interpreted as mean difference in log-transformed epicardial adipose tissue (EAT) volume (cm^3). Positive values indicate increases and negative values indicate decreases in log-transformed EAT volume in exploratory variable. HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein. Bold values represent significant *P*-values.
[a]Abnormal waist circumference was defined as at least 80 cm in female individuals and at least 90 cm in male individuals.
[b]HCV co-infection was defined as positive HCV antibody.

associated with EAT volume (Table 1). Moreover, higher CAC score (>100 vs. <100), but not and liver stiffness, was independently associated with EAT volume in all four multivariable models, adjusted for the confounders.

Discussion

In this current study that we utilized the advantages of aging cohort, older PWH had significantly higher EAT volume than HIV-negative older adults. After adjusting the traditional and metabolic risk factors, HIV infection was independently associated with higher EAT volume. In addition, male sex, insulin resistance and central obesity were associated with EAT volume. Duration of HIV infection was also independently associated with EAT among PWH although there were no significant associations of other HIV-related parameters, such as $CD4^+$ count and types of antiretroviral drugs.

Like previous studies in both HIV-positive and HIV-negative populations, our study confirmed the independent association of traditional risks, such as older age, male

Table 4. Multivariable linear regression analysis on log-transformed epicardial adipose tissue volume in HIV-positive participants (*N* = 339).

	Univariate analysis			Multivariate analysis		
HIV-related parameters	Coefficient	95% CI	*P* value	Coefficient	95% CI	*P* value
Male (vs. female)	0.08	−0.01 to 0.16	0.059	0.10	0.01–0.19	**0.033**
Age (per 1 year increase)	0.02	0.01–0.03	<0.001	0.02	0.01–0.02	**<0.001**
HOMA-IR (≥2 vs. <2)	0.18	0.10–0.27	<0.001	0.10	0.02–0.19	**0.011**
Abnormal waist circumference[a] (yes vs. no)	0.27	0.19–0.35	<0.001	0.12	0.04–0.19	**0.002**
Abnormal triglyceride at least 150 mg/dl	0.22	0.14–0.30	<0.001	0.05	−0.04 to 0.13	0.294
Smoking status (ever smoke vs. never smoke)	0.07	−0.02 to 0.15	0.112	0.24	0.16–0.32	**<0.001**
Hypertension (yes vs. no)	0.16	0.08–0.24	<0.001	0.01	−0.07 to 0.09	0.775
Diabetes mellitus (yes vs. no)	0.12	0.02–0.23	0.023	−0.08	−0.18 to 0.02	0.135
Current statin use (yes vs. no)	0.14	0.05–0.22	0.002			
Nadir $CD4^+$ cell count (<100 vs. ≥100 cells/μl)	0.05	−0.04 to 0.14	0.277			
Current $CD4^+$ cell count (<500 vs. ≥500 cells/μl)	0.00	−0.09 to 0.09	0.996			
Current $CD4^+/CD8^+$ ratio (≥1 vs. <1)	0.01	−0.02 to 0.05	0.512			
Duration of HIV (>15 vs. <15 years)	0.16	0.06–0.25	0.002	0.10	0.01–0.19	**0.028**
Duration of ART (>15 vs. <15 years)	0.10	0.01–0.18	0.021			
Current ART regimen			0.380			
NNRTI	Ref					
PI	0.06	−0.03 to 0.15	0.220			
Other	0.06	−0.06 to 0.19	0.336			
Lipodystrophy (yes vs. no)	0.12	0.03–0.20	0.006	0.05	−0.03 to 0.12	0.253
Stavudine exposure (yes vs. no)	0.08	−0.01 to 0.16	0.166			
Abacavir exposure (yes vs. no)	0.10	−0.05 to 0.25	0.187			

Coefficients can be interpreted as mean difference in log-transformed epicardial adipose tissue (EAT) volume (cm^3). Positive values indicate increases and negative values indicate decreases in log-transformed EAT volume in exploratory variable. Bold values represent significant *P*-values. ART, antiretroviral therapy; HOMA-IR, homeostatic model assessment for insulin resistance; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitors.

sex and several metabolic and CVD risk factors, such as insulin resistance and central obesity. Previous analyses from HIV cohorts of men with HIV showed the higher EAT volume in PWH than the HIV-negative controls [15,20], although this difference was not seen in a cohort, which compared EAT volume between asymptomatic HIV-positive and HIV-negative women [14]. Our study results are in line with the reports showing that men had higher EAT volume than women [21,22].

As EAT was linked to inflammation and atherosclerosis risks, which is influenced by central obesity and hyperlipidemia, previous studies have also demonstrated the pleiotropic effects of statins on the reduction of epicardial fat tissue volume or attenuation in the general population [23,24]. However, a recent longitudinal study has shown that there were no changes in EAT volume with the baseline statin use [25]. A post hoc analysis of a randomized controlled trial (RCT) of rosuvastatin treatment among PWH on stable ART showed that HOMA-IR was independently correlated with baseline pericardial fat density and volume despite no association was found between the statin therapy and the change in pericardial adipose tissue volume or density [26]. In our study, insulin resistance and central obesity was positively associated with EAT volume independent of metabolic, CVD risk factors and HIV serostatus. These results confirmed the association of visceral adiposity or EAT volume with insulin resistance in both PWH and non-HIV populations reported previously [15,27,28], suggesting the impacts of visceral adipose tissue on glucose metabolism.

Subclinical coronary atherosclerosis as determined by CAC was also found to be associated with higher EAT volume. The results echoed previous studies, which found similar findings in PWH [21] and the general population [9]. Coronary calcification remained a significant predictor for EAT volume after adjusting for demographics, HIV status and other cardiometabolic risk factors in our study. Previous reports have also demonstrated the association of epicardial fat and high-risk coronary plaque [14,15,29], possibly resulted from the inflammatory reactions in the local tissues of the arteries. However, we were not able to identify an association of high-risk plaques with EAT volume because of a lack of data on volumetric analysis and information on plaque sub-types. Nonetheless, epicardial fat volume from cardiac CT images, which are generally obtained in clinical settings for evaluating CAC scoring, can be used a useful tool for screening and stratifying risks for CVD development among PWH population. The association of atherosclerotic risk with epicardial fat highlights the prognostic value of EAT and the potential application of targeted interventions with novel therapeutic agents, such as anti-inflammatory therapies to prevent the serious clinical outcomes in PWH population.

Our study results also confirm the previous evidence that EAT volume was affected by HIV infection, and it is associated with duration of HIV [20,22,30]. This confirms the previous study suggesting that PWH had distinct features from HIV-negative individuals in addition to the traditional cardiometabolic risk factors, which are associated with the formation of ectopic fat deposition through multiple mechanisms including persistent inflammation and immune activation [29]. Despite the lack of evidence for the association of ART, such as D4T and ABC in our PWH model, other studies have described that certain ART drugs were associated with increased pericardial fat volume [22]. Our study results provide additional information on the growing evidence that longer duration of HIV infection may be associated with visceral adiposity including epicardial fat [20], which may potentially increase the risks of coronary atherosclerosis through inflammatory mediators [9].

Although EAT and visceral fat, such as liver fat share the same embryonic origin of brown adipose tissue [13] and have the common risk factors, such as insulin resistance and cardiometabolic risks, the association of EAT with liver steatosis has been controversial in non-HIV patients [11,31] and it has not been studied in older PWH population. Previous studies examining the association between EAT and fatty liver in PWH, have demonstrated inconsistent results, with one study suggesting a relationship between EAT and surrogate markers of fatty liver, whereas the other study failed to find an association. A possible reason for this discordancy was the relatively small number of study participants, and a comparatively younger population of PWH compared with our study [32,33]. A possible reason for this discordancy was the relatively small number of study participants, and a comparatively younger population of PWH compared with our study. However, both studies have found a relationship between EAT and visceral adipose tissue. One novel finding from our study was that higher EAT volume was found in participants with severe liver steatosis, assessed by noninvasive imaging than those without steatosis in PWH. This suggests the potential interaction between liver and epicardial fat, and the burden of those visceral adiposity on cardiovascular disease risks in HIV-positive population needs further exploration. Despite the unclear mechanisms for the association of liver steatosis with EAT, one possible speculation is that increased EAT could enhance the production of proinflammatory cytokines promoting the progression of liver steatosis [34].

Our study has several limitations to be acknowledged. This is a cross-sectional analysis; therefore, from our findings, causality could not be inferred. We also did not include visceral adipose tissue and subcutaneous adipose tissue compartments, and instead, we used waist circumference measurement to assess the central/abdominal obesity. In addition, PWH participants included were well treated, and majority were virologically suppressed at the time of evaluation, hence, the impact of HIV viral

load could not be assessed. However, this allowed us to investigate the relationship of other HIV-related parameters with EAT volume without the impact of HIV viremia among virologically suppressive PWH. All the study participants, regardless of HIV serostatus, were older than 50 years and the generalizability of the study findings to younger population might be limited. In addition, data were not available for different adipokines and biomarkers, such as serum leptin, adiponectin and insulin-like growth factor 1 (IGF-1) in our study. Therefore, the association of those biomarkers with EAT could not be evaluated. Data on dietary practices and exercise routines were not available from participants in our study population, so unobserved confounding from these variables cannot be ruled out. Despite these limitations, one of the strengths of our study is that it included large proportion of female participants, compared with the previous reports, which were predominantly men. To our knowledge, this is the first study to evaluate the liver components, such as fibrosis and steatosis in evaluating epicardial fat among older PWH population.

In conclusion, HIV infection was independently associated with higher EAT volume in an aging cohort, and our study demonstrates the association of EAT volume with insulin resistance, central obesity, liver steatosis and coronary calcium. In older Asian PWH with HIV suppression, duration of HIV was associated with EAT volume. Higher EAT volume was also found in PWH with severe liver steatosis, and further studies to confirm such associations and its clinical impacts among PWH population are needed.

Acknowledgements

We would like to thank all the participants and the staffs, especially Ms Khuanruan Supakawee and Ms Jaravee Jirapasiri, involved in this study.

Financial support: this study was supported by the Higher Education Research Promotion and National Research University Project of Thailand, Office of the Higher Education Commission, and Chulalongkorn University, Project code NRU59-(014)-HR. Coronary artery calcium scoring was performed with the support of Ratchadapiseksompotch Fund (#RA59/082).

Authors' contributions: M.T., W.M.H., K.T., P.C., S.S., T.A., T.U., S.J.K., S.B., A.A. contributed to design and concept of the study analysis. M.T., K.T. conducted the epicardial fat analysis and data collection. P.C., S.S., W.M.H., T.U., S.B., A.A. contributed to patient care. M.T., T.A., W.M.H., S.J.K., A.A. contributed to interpretation of the study results. T.A., W.M.H. performed statistical analysis. M.T., W.M.H. wrote the first draft of the article. W.M.H., A.A., S.J.K. critically reviewed the manuscript. All authors contributed to interpreting the findings and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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