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Epicardial Fat is Associated with Duration of Antiretroviral Therapy and Coronary Atherosclerosis: The Multicenter AIDS Cohort Study

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Abstract

Objective—Cytokines released by epicardial fat are implicated in the pathogenesis of atherosclerosis. HIV infection and anti-retroviral therapy have been associated with changes in body fat distribution and coronary artery disease. We sought to determine if HIV infection is associated with greater epicardial fat and if epicardial fat is associated with subclinical coronary atherosclerosis.

Design—We studied 579 HIV-infected and 353 HIV-uninfected men age 40 to 70 years with non-contrast computed tomography (CT) to measure epicardial adipose tissue volume (EAT) and

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coronary artery calcium (CAC). Total plaque score (TPS), and plaque subtypes (non-calcified, calcified and mixed) were measured by coronary CT angiography in 706 men.

Methods—We evaluated the association between EAT and HIV serostatus, and the association of EAT with subclinical atherosclerosis, adjusting for age, race and serostatus and with additional cardiovascular (CV) risk factors and tested for modifying effects of HIV serostatus.

Results—HIV-infected men had greater EAT than HIV-uninfected men (p=0.001). EAT was positively associated with duration of antiretroviral therapy (p=0.02), specifically AZT (p<0.05). EAT was associated with presence of any coronary artery plaque (p=0.006) and non-calcified plaque (p=0.001), adjusting for age, race, serostatus and CV risk factors. Among men with CAC, EAT was associated with CAC extent (p=0.006). HIV serostatus did not modify associations between EAT and either CAC extent or presence of plaque.

Conclusions—Greater epicardial fat volume in HIV-infected men and its association with coronary plaque and antiretroviral therapy duration suggest potential mechanisms that might lead to increased risk for cardiovascular disease in HIV.

Keywords

Imaging; plaque; risk factors; HIV; ART

Introduction

Infection with Human Immunodeficiency Virus (HIV) and treatment with anti-retroviral therapy (ART) have been implicated in the pathogenesis of coronary heart disease (CHD).[1-5] Questions remain as to the mechanisms by which HIV infection or its treatments might lead to CHD. The use of ART is accompanied by changes in fat distribution and metabolic abnormalities including insulin resistance, and proatherogenic serum lipid changes.[6, 7] Expanding or altered visceral fat depots may play a role in facilitating atherosclerosis. These visceral fat depots are metabolically active and harbor an inflammatory milieu that promotes atherosclerosis. Epicardial fat, in particular, may play a unique role in atherosclerosis because of its close proximity to the coronary vessels, thus serving as a local source of proinflammatory cytokines. An association between increased epicardial fat and incident CHD and coronary atherosclerosis has been demonstrated in the general population.[8, 9]

A few studies have examined epicardial fat and CHD in the HIV-infected population and have generated conflicting findings. In a study of 110 participants, Lo et al. found increased epicardial fat in HIV-infected participants compared with HIV-uninfected controls, but found no correlation between epicardial fat and coronary plaque volume, segments with plaque or with coronary calcium score measured by computed tomography. [10, 11] Iacobellis et al demonstrated an association between echocardiographic measures of epicardial fat thickness and carotid intima media thickness in 103 HIV patients on HAART with the metabolic syndrome.[12] More recently, Guaraldi and colleagues conducted a larger study and confirmed the presence of greater epicardial fat depots in HIV-infected participants, and also demonstrated an association between epicardial fat and increased coronary artery calcium (CAC).[13] The conflicting conclusions from these initial studies require further study.

To investigate the relationship between epicardial fat and HIV infection and the association between epicardial fat and subclinical coronary atherosclerosis and plaque composition, we measured CAC from non-contrast computed tomography (CT) scans and coronary artery plaque extent and composition with contrast-enhanced coronary CT angiography (CCTA) in participants from the Multicenter AIDS Cohort Study (MACS), a large, prospective multiethnic cohort of both HIV-infected and HIV-uninfected men who have sex with men (MSM). CAC is known to be a potent predictor of coronary events in both symptomatic and asymptomatic populations.[14, 15] CCTA provides more detailed characterization and measurement of plaque burden beyond calcium scoring and allows identification of plaque subtypes that may carry differential risks for adverse cardiovascular events.[16-19] We hypothesized that HIV-infected men have more epicardial fat than HIV-uninfected controls, and that epicardial fat is associated with subclinical coronary artery atherosclerosis.

Methods

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective observational study that enrolled MSM in four major United States cities: Baltimore, MD/ Washington, DC, Chicago, IL, Los Angeles, CA, and Pittsburg, PA. Active MACS participants between the ages of 40 and 70, without a history of prior cardiac surgery, percutaneous transluminal coronary angioplasty (PTCA) or stent placement, and who weighed less than 300 pounds were invited to undergo non-contrast CT scanning. Coronary CT angiography was performed at the time of scanning on men without contrast allergy, atrial fibrillation, or impaired renal function (estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 within 30 days of scanning or during any previous MACS examination). All participants gave informed consent to participate. This study was approved by the Institutional Review Board of each institution.

Imaging Parameters

Non-contrast CT and CCTA were performed using multi-detector scanners at each site as previously described.[20] Non-contrast cardiac CT scans and a single imaging slice of the abdomen at the level of the fourth lumbar vertebra were performed to measure CAC and adipose tissue volumes, including epicardial adipose tissue volume (EAT), pericardial adipose tissue volume (PAT), intrathoracic adipose tissue volume (IAT), and abdominal visceral fat volume (AVF).

CAC scans included a minimum of 40 slices, spaced 2.5-3.0 mm apart, starting from 1 cm below the carina. CAC scores were computed using the Agatston method. [21] Adipose tissue measurements were performed on axial slices of non-contrast images of the heart using GE Advantage 4.6 Workstations (GE Healthcare, Waukesha, WI). EAT was defined as the adipose tissue between the surface of the heart and visceral pericardium and was measured on axial images from 10mm above the superior extent of the left main ostium to the last slice containing part of pericardial sac. EAT was measured by manually tracing the pericardium every 2-3 slices below the start point and software automatically tracing out the segments in between selected slices. PAT extended from outside the visceral pericardium to the chest wall. Intrathoracic adipose tissue (IAT) measurement was performed using the

same superior boundary, the diaphragm as the inferior boundary, the chest wall as the anterior boundary and the aorta, bronchi and esophagus defined the posterior boundary. Adipose tissue present in the posterior mediastinum and para-aortic adipose tissue was not included in the IAT measurements. Volume analysis software was used to discern fat from other tissues using a threshold of -190 to -30 Hounsfield Units. Abdominal visceral fat was measured from an axial slice of the abdominal non-contrast CT scan images. The reader traced the parietal peritoneum border at the level of L4-L5 inter-space and fat was defined as the intra-peritoneal area of the abdominal cavity within -190 to -30 Hounsfield Units. Adipose tissue measurements were performed by 3 well-trained readers, blinded to participant characteristics. Inter-observer and Intra-observer agreement of EAT and IAT measurement was highly reproducible.[22]

Eligible participants underwent CCTA using radiation dose reduction techniques. Beta-blocker therapy could be given prior to scanning to reduce heart rates to improve image quality, and sublingual nitroglycerin was given immediately before contrast injection unless contraindicated. The images were reviewed on a 3-dimensional image analysis workstation (GE Advantage Workstation, GE Healthcare) at the central reading location (Torrance, CA) by 2 experienced observers unaware of the participant's clinical history. Plaque grading was performed according to the American Heart Association's 15-segment coronary artery classification grading system.[23] The segments were evaluated for the presence or absence of coronary plaque using axial and curved multiplanar reconstruction with one coronary plaque type assigned per segment. Plaques were defined as structures > 1 mm^2 within and/or adjacent to the vessel lumen that could be clearly distinguished from the lumen and surrounding pericardial tissue. Noncalcifed plaque was defined as any structure associated with the coronary wall with CT attenuation below that of the lumen but above that of the surrounding connective tissue and epicardial fat. Calcified plaque was defined as any structure greater than 130 HU visualized separately from the coronary lumen. Within each segment plaques with calcified tissue comprising > 50% of the plaque area were classified as calcified, plaques with some but < 50% calcium were considered mixed, and plaques without any calcium were classified as noncalcified lesions. Plaque size was scored as none(0), mild(1), moderate(2) or severe(3). Semiquantitative measures of overall coronary artery plaque burden were derived. The total calcified plaque score (CPS), mixed plaque score (MPS) and non-calcified plaque score (NCPS) were the sum of the scores of all identified calcified, mixed and noncalcified plaques, respectively. The total plaque score (TPS), was the sum of the NCPS, MP and CPS, and was the summary measure of overall plaque burden.[24]

Metabolic, Biochemical, and Immunologic Parameters

MACS participants undergo semi-annual follow-up with a history and physical examination. From these visits, demographic and clinical data from the visit closest to the scan date were obtained (generally within 6 months of the CT visit) including measures of HIV disease activity in HIV-infected participants, including plasma HIV RNA levels (peak and present), $CD4^+$ T-cell count (present and nadir), history of AIDS, and duration of highly active anti-retroviral therapy (HAART) use. Fasting blood samples were obtained to measure serum levels of glucose, insulin, total cholesterol, high-density lipoprotein cholesterol (HDL), and

triglycerides. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation or was measured directly in persons with triglyceride levels greater than 400 mg/dl or a non-fasting sample. Creatinine was measured within 30 days of the CT scan with contrast for the calculation of estimated glomerular filtration rate using the MDRD equation.[25]

Statistical Analysis

Exploratory data analysis was performed to compare the distribution of potential confounders and mediators in HIV-infected and HIV-uninfected men using the Wilcoxon rank-sum test or chi-square test, where appropriate. Due to a high prevalence of zero scores for many plaque variables, the first analysis dichotomized the study population by presence or absence of plaque, with plaque presence defined as a score greater than zero. Separate multiple logistic regressions were used to evaluate the association between epicardial fat and plaque presence for CAC, TPS, CPS, MPS and NCPS, adjusting for age, race and HIV serostatus (minimally adjusted models). Nested multivariable analyses were performed with sequential additional adjustment for established cardiovascular risk factors (systolic blood pressure, history of hypertension, diabetes mellitus, fasting glucose levels, triglyceride levels, use of lipid lowering medications and smoking). The cardiovascular risk factors included in the multivariate model were selected from variables which when individually added to the minimal model had a p-value ≤ 0.1 and when added to a multivariate model maintained a p-value < 0.1. To assess whether any association between epicardial fat volume and plaque was independent of other measures of adiposity (body mass index (BMI) and/or abdominal visceral adipose tissue volume by CT scan), the multivariate models were further adjusted for BMI or abdominal visceral fat. HIV modification of each association was assessed by inclusion of appropriate interaction terms. Missing values were imputed five times based on the distribution of covariates using a Markov chain Monte Carlo (MCMC) method assuming multivariate normality. Values for the following number of men were missing and imputed for multiple regression analyses: Hypertension medications (3), body mass index (17), diabetes medications (3), smoking pack-years (2), lipid medications (11), triglyceride (40), systolic blood pressure (33), fasting glucose (37).

Linear regression was used to assess the relationship of epicardial fat with plaque extent (burden) among individuals with plaque present (i.e., plaque score greater than zero) for each of CAC, TPS, CPS, MPS and NCPS after adjusting for age, race and HIV serostatus. Plaque scores were natural-log transformed. Multivariable linear regression was performed using serial models as described for plaque presence.

We used robust regression to analyze epicardial fat volumes and traditional CHD risk factors, and associations with HIV parameters. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Statistical significance was established at a p-value < 0.05.

Results

Participant Characteristics

There were 932 men with complete non-contrast CT imaging who were included in this analysis. 706 of these men (75.8%; 422 HIV-infected and 284 HIV-uninfected) underwent CCTA. The HIV-infected participants were younger, had a lower mean BMI than their seronegative counterparts and were less likely to be Caucasian (all $p<0.001$) (Table 1). In unadjusted analyses current tobacco use was more prevalent among HIV-infected individuals ($p=0.004$), while HIV-uninfected men were more likely to be former tobacco users. Compared to HIV-uninfected men, HIV-infected participants were more likely to use lipid-lowering medications (36.3% vs. 29.7%, $p=0.04$). HIV-infected participants had significantly higher fasting triglyceride levels and lower HDL (both $p<0.001$) and LDL cholesterol levels ($p=0.002$) compared to HIV-uninfected men. Fasting glucose levels and prevalence of diabetes were similar by serostatus but HIV-infected men had higher fasting insulin levels ($p < 0.001$). Differences in age, serum creatinine, fasting glucose, diabetes, insulin, LDL-C and hypertension medication use were apparent when comparing individuals who underwent CCTA to persons who did not.

Among HIV-infected men, 95.9% had initiated HAART before undergoing CCTA with a median duration of 12.5 (IQR 8.8-14.1) years (Table 1). A history of an AIDS illness was present in 13.8% of men. HIV RNA level was undetectable (<50 copies/mL) in 80.9% and the median HIV RNA among men with a detectable level was 565 (IQR 150-9070) copies/mL. The median CD4+ T-cell count was 599 (IQR 423-749) cells/mm^3 and the median nadir CD4+ T-cell count was 243 (IQR 133-331) cells/mm^3.

Epicardial Fat and Associations with HIV Serostatus, HAART, CV Risk Factors and Metabolic Parameters

HIV-infected men had a significantly greater volume of epicardial adipose tissue than HIV-uninfected men after adjusting for age and race (median values: 125 (IQR 93-131) cm^3 vs. 115 (IQR 81-120) cm^3, $p=0.001$). In separate multivariate models adjusted for age, race and HIV serostatus, increased epicardial fat volume was associated with greater BMI, antihypertensive medication use, use of lipid lowering medication, higher fasting glucose, higher insulin levels and use of diabetes medications(all $p<0.001$). Among men not taking lipid medications, higher triglyceride levels ($p=0.0003$) and lower HDL cholesterol ($p=0.02$) were associated with more epicardial fat after adjusting for age, race and serostatus. There were no associations with cumulative tobacco use ($p=0.18$) or total ($p=0.10$) or LDL cholesterol ($p=-0.35$). Among men not taking hypertension medications, systolic ($p=0.004$) and diastolic ($p=0.006$) blood pressure were associated with more epicardial fat. When the significant covariates ($p<0.05$) were included in a single multivariable model to predict epicardial fat, there were significant associations with BMI, use of lipid medications (both $p<0.001$), and triglycerides ($p=0.04$), There were borderline independent associations with cumulative tobacco use ($p=0.09$) and no independent associations with use of diabetes or hypertension medications, fasting glucose or insulin, or systolic blood pressure (all $p>0.10$).

Among HIV-infected men, after adjustment for age, race and CV risk factors, EAT volume was positively associated with the duration of HAART (estimate 1.15per year, p=0.02) (Table 2). Duration of use of azidothymidine (AZT) therapy was associated with greater EAT volume after adjustment for age, race and CV risk factors (estimate 0.94 per year, p=0.048). In contrast, there were no associations between duration of use of either protease inhibitors, stavudine (d4T), or abacavir (ABC) therapy.

Epicardial Fat and Plaque Burden

Epicardial fat volume was moderately correlated with pericardial fat and intraabdominal visceral fat volumes (r=0.67 and r=0.67, respectively, p<0.0001) and strongly correlated with total intrathoracic fat volume (r=0.88, p<0.0001). Generally associations between epicardial fat and coronary plaque were similar but somewhat stronger than with PAT or IAT, and therefore, results are only presented for EAT.

Coronary calcium was present in 53.0% of men. Among the 706 men who underwent CCTA, 77.2% had coronary plaque present (TPS>0), with an unadjusted prevalence of 78.2% among HIV-infected and 75.7% among HIV-uninfected men. Non-calcified plaques were present in 59.9% overall. The HIV-infected men had a greater prevalence (p=0.004) and extent (p=0.001) of non-calcified plaque in unadjusted analyses (Table 3).

Adjusted associations between EAT and the presence and extent of plaque (CAC, NCPS, CPS, MPS and TPS) are presented in tables 4 and 5. After adjustment for age, race and HIV serostatus, with increasing EAT there was an increase in the odds of CAC (OR 1.04 per 10 cm^3 increase in EAT, p=0.003), any plaque being present on CCTA (OR 1.09, p<0.001), non-calcified plaque (OR 1.06, p<0.001), and calcified plaque (OR 1.03, p=0.037). These associations remained statistically significant after further adjustment for cardiovascular risk factors for any plaque on CCTA (p=0.006) and non-calcified plaque (p=0.001) (as listed in the tables). Additional adjustment for BMI or abdominal visceral fat did not significantly attenuate these associations. There were no interactions by HIV serostatus for any of these associations (p>0.40). Associations between increasing EAT and presence of plaque stratified by HIV serostatus are presented in supp Table 4a and 4b.

In linear regression models restricted to men with any plaque present (i.e. plaque scores>0), after adjustment for age, race and HIV serostatus, increasing EAT was associated the extent of CAC (β-coefficient = 0.048 log CAC score per 10 cm^3 increase in EAT, p<0.001, and extent of any plaque on CCTA (β=0.021, p=0.001) (Table 5). There was also a trend with extent of non-calcified plaque ((β=0.011, p=0.06). After additional adjustment for CV risk factors including BMI or abdominal visceral fat, increasing EAT remained significantly associated with extent of CAC. The association between extent of any plaque in minimally adjusted models was no longer significant after further adjusting for CV risk factors. (Table 5). There were no significant interactions by HIV serostatus for any of these associations (p>0.10). The fully adjusted associations between EAT and extent of CAC were significant in HIV-infected men (β=0.067, p<0.001) but not in HIV-uninfected men (β=0.009, p=0.78), but the HIV interaction p value was not significant (p=0.23). Associations between increasing EAT and extent of plaque stratified by HIV serostatus are presented in supp Table 5a and 5b).

Discussion

In a well-characterized cohort of men with or at risk for HIV infection we found that HIV infection was associated with increased epicardial adiposity. Duration of HAART use and treatment with AZT were associated with increased epicardial fat among HIV-infected men, whereas other markers of HIV disease stage and control and other ART drugs showed no association. Additionally, epicardial tissue volume was associated with subclinical coronary atherosclerosis, which was independent of other measures of adiposity including BMI and abdominal visceral fat volume. Epicardial fat was associated with the presence of any plaque and of non-calcified plaque and the extent of CAC, and these associations remained after adjusting for cardiovascular risk factors. The associations of epicardial fat with coronary plaque did not significantly differ by HIV serostatus. The greater volume of epicardial fat in HIV-infected men and its association with coronary plaque and duration of HAART use may suggest potential mechanisms that might lead to increased risk for cardiovascular disease in patients with HIV.

In our study we confirmed the independent association of epicardial fat with numerous cardiovascular risk factors and elements of the metabolic syndrome. The difference in epicardial fat between HIV-infected and uninfected men persisted even after adjustment for these well-established risk factors, suggesting an additional mechanism beyond traditional risk factors to explain the difference.

Strengths of our study include the large sample size and use of CCTA evaluation that allowed detailed assessment of plaque morphology among HIV-infected and uninfected men. In addition, we measured the full epicardial fat volume which is a more reproducible and superior measure than epicardial fat thickness and we defined epicardial fat separately from pericardial fat by identifying the pericardial sac.[26] Furthermore, our study addresses many of the limitations of the two previous studies conducted on this subject. For example, although Guaraldi and colleagues studied a large group of HIV-infected participants, they did not include an HIV-uninfected control group. In contrast, Lo and colleagues' study incorporated HIV-uninfected controls, but was limited by a smaller sample size. Our study utilized the strengths of a large cohort of HIV-infected and HIV-uninfected men with similar environmental exposures (all are men who have sex with men).

The use of CCTA in addition to calcium scoring further distinguishes our study and adds to our ability to characterize subclinical atherosclerotic lesions. This modality allowed examination of both calcified and non-calcified plaques, which is of interest since non-calcified plaques are earlier atherosclerotic lesions that may have a greater necrotic lipid core. Identification of these non-calcified plaques, in addition to calcified plaque seen with non-contrast CT scans, allows more accurate characterization of a participant's total plaque burden.[27] We and others have demonstrated that HIV-infected men are more likely to have non-calcified plaque than calcified plaque.[28, 29] Studies have demonstrated that non-calcified plaques are more prone to rupture than calcified plaques, leading potentially to acute coronary syndromes.[30, 31] Thus, from a design perspective, our study combines the best features of the previous investigations and attends to their shortcomings with a large

sample size, an adequate control population, and advanced coronary atherosclerosis imaging technology.

Studies have demonstrated an independent association between EAT and coronary atherosclerosis, and suggested EAT as a risk factor for accelerated progression of subclinical coronary atherosclerosis in the general population.[32-35] However results were conflicting in patients with HIV.[10, 13] Our study adds to the growing evidence that HIV-infection may affect vascular health. HIV-infection and/or its treatment may cause an alteration in the distribution of visceral adipose tissue including the epicardium. When adipose tissue envelops the coronary arteries, it may exert a damaging paracrine effect possibly via a milieu of cytokines that promotes inflammation, vessel damage and leads to resultant atherosclerosis.[36] Our study profiles the early stages of this effect by examining subclinical atherosclerosis parameters like coronary artery calcium and plaque characteristics, which have been shown in the general population to predict cardiovascular events.[14]

Despite these strengths, our study has some limitations. This is a cross-sectional analysis and thus no causality can be inferred from our findings. Given that most of the HIV-infected men were on treatment, we were unable to segregate the effects of HIV-infection and anti-retroviral therapy in our analyses. Therefore, we cannot claim with certitude which of the two is largely responsible for the findings of increased epicardial adiposity. Additionally, this study was conducted only in men and it is unknown whether these findings can be generalized to women.

Conclusion

In summary, among men with or at risk for HIV infection, increased epicardial fat deposition is associated with HIV infection, duration of treatment with HAART, and more plaque in the coronary arteries. Further studies are needed to investigate which additional aspects of HIV infection or its treatment are responsible for increased epicardial adiposity, potential therapies to reduce epicardial fat, and whether greater EAT increases risk for cardiovascular events in HIV patients.

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AIDS. Author manuscript; available in PMC 2015 July 17.

Table 1

Characteristics of the Study Population

	HIV Seropositive	HIV Seronegative	p-value*	CT with contrast	Non-contrast CT only	p-value†
N	579	353		706	226	
Age (years)	53.4(6.5)	55.9(7.3)	<0.001	54.0(7.0)	55.3(6.6)	0.01
Race			<0.001			0.62
Caucasian (%)	54.1	68.6		59.1	61.1	
African-American (%)	32.8	23.8		29.3	29.6	
Hispanic/Other (%)	13.1	7.6		11.6	9.3	
Hypertension (%)	49.0	47.7	0.70	46.5	54.8	0.03
Hypertension medications (%)	35.3	33.6	0.60	31.7	43.8	0.001
Diabetes (%)	13.7	10.0	0.11	10.5	17.9	0.004
Diabetes medications (%)	9.2	7.4	0.35	7.3	12.4	0.02
Tobacco use			0.004			0.19
Never smoker (%)	25.8	24.6		25.0	26.5	
Current smoker (%)	30.8	22.0		26.2	31.4	
Former smoker (%)	43.4	53.4		48.8	42.2	
Body Mass Index (kg/m^2)	26.1(4.4)	27.5(4.9)	<0.001	26.6(4.5)	26.7(5)	0.75
Glucose (mg/dL)	102.8(25)	101.9(31.9)	0.16	101.0(24.3)	107.2(36.7)	0.01
Insulin (μIU/mL)	17.3(14)	15.1(12.2)	<0.001	15.4(9.9)	19.9(20.7)	0.005
Total Cholesterol (mg/dL)	188.3(43.1)	191.6(36.4)	0.13	189.2(39.1)	190.6(45.5)	0.64
LDL Cholesterol (mg/dL)	105.9(35.8)	112.3(32.2)	0.002	109.4(34.4)	105.0(35.0)	0.03
HDL Cholesterol (mg/dL)	48.2(16.0)	52.7(16.3)	<0.001	49.8(15.9)	50.3(17.3)	0.97
Triglycerides (mg/dL)	174.6(131.1)	127.6(78.2)	<0.001	150.8(101.7)	176.5(153.0)	0.054
Lipid lowering medications (%)	36.3	29.7	0.04	33.4	34.8	0.70
Serum Creatinine (mg/dL)	1.1(0.5)	1.0(0.2)	0.03	1.0(0.2)	1.3(0.7)	<0.001
Among HIV Seropositive	**N = 579**			**N = 422**	**N =157**	
Viral Load undetectable, < 50 copies/mL (%)	80.9	-		79.9	83.6	0.33
Viral Load (copies/mL)**	565(150-9070)	-		611(125-10053)	537(189-5939)	0.97
CD4$^+$ T-cell count (cells/mm^3)	599(423-749)	-		600(431-749)	579(408-748)	0.51
CD4$^+$ T-cell count nadir (cells/mm^3)	243(133-331)	-		253(155-339)	206(95-312)	0.006

	HIV Seropositive	HIV Seronegative	p-value*	CT with contrast	Non-contrast CT only	p-value†
Initiated HAART (%)	95.9	-		95.3	97.5	0.24
Duration of HAART (years)	12.5(8.8-14.1)	-		12.2(8.5-14)	13.1(9.7-14.4)	0.03
History of AIDS (%)	13.8	-		10.9	21.7	0.001

Data are presented stratified by HIV serostatus for the entire cohort and then stratified by whether or not a CT with contrast was performed. Laboratory results represent fasting levels. Data are reported as mean (standard deviation) or percentage or median (1^{st} quartile – 3^{rd} quartile). P values are unadjusted.

* P value comparing seropositive and seronegative values.

† P value comparing CT with contrast versus non-contrast only values.

** Among 108 HIV+ men with detectable viral load (>50 copies/mL)

AIDS. Author manuscript; available in PMC 2015 July 17.

Table 2

Epicardial Adipose Tissue Volume Associations with HIV-disease related parameters in HIV-infected Men (n= 579)

	Effect estimate (95% CI)	p-value
Years since HAART initiation (per 1 year increase)	1.15(0.17,2.14)	0.02
Protease Inhibitor Therapy (per year)	0.38(-0.49,1.25)	0.40
Azidothymidine (AZT) Therapy (per year)	0.94(0.01,1.87)	0.048
Stavudine (d4T) therapy (per year)	-0.31(-1.81,1.18)	0.68
Abacovir (ABC) therapy (per year)	0.26(-1.09,1.61)	0.71
ART therapy Pre-HAART (yes vs. no)	-1.52(-10.21,7.17)	0.73
Undetectable Viral load (yes vs. no)*	7.32(-3.43,18.07)	0.18
Viral Load (log 10) †	-3.73(-10.82,3.37)	0.30
Peak Viral load (log 10)	2.31(-2.48,7.11)	0.34
Pre-HAART Viral load (log 10)	3.64(-0.16,7.43)	0.06
Current CD4 count (per 100 cell increase)	0.49(-1.12,2.10)	0.55
Nadir CD4 count (per 100 cell increase)	-0.66(-3.3,1.98)	0.63
Pre-HAART CD4 count (per 100 cell increase)	-0.89(-2.73,0.95)	0.35
History of AIDS (yes vs. no)	-1.44(-13.36,10.48)	0.81

*Defined as viral load < 50 copies/ml compared to those with viral load>50 copies/ml.

†Among men with detectable viral load. All analyses are adjusted for age, race and CAD risk factors including use of antihypertensive medications, systolic blood pressure (among those not on antihypertensive medications), use of diabetes medications, fasting glucose (among those not on diabetes medications), use of lipid medication use, triglyceride levels (among those not on lipid medications) and smoking (cumulative pack years). HAART= highly active anti-retroviral medical therapy

AIDS. Author manuscript; available in PMC 2015 July 17.

AIDS. Author manuscript; available in PMC 2015 July 17.

Table 3

CT Scan Results

Non-contrast CT Scan Parameters	HIV Seropositive N=579	HIV Seronegative N=353	Total N=932	p-value*
Epicardial Adipose Tissue Volume (mm^3)	121(60)	114(52)	119(58)	0.23
Pericardial Adipose Tissue Volume (mm^3)	125(84)	126(85)	125(84)	0.995
Intrathoracic Adipose Tissue Volume (mm^3)	246(132)	240(127)	244(130)	0.48
Abdominal Visceral Adipose Volume (mm^3)	164(97)	160(93)	162(95)	0.58
Coronary Artery Calcium Present: Agatston Score > 0 (%)	53.2	52.6	53.0	0.85
Coronary Artery Calcium Score among those with calcium present (n=493)	72(23-194)	80(20-257)	73(22-211)	0.45
Contrast-enhanced CT Scan Parameters	N=422	N=284	N=706	
Prevalence of any coronary plaque (%)	78.2	75.7	77.2	0.44
Prevalence of non-calcified plaque (%)	64.2	53.5	59.9	0.004
Prevalence of calcified plaque (%)	34.4	40.1	36.7	0.12
Prevalence of mixed plaque (%)	34.8	32.4	33.9	0.50
Total Plaque Score (TPS)	3(1-5)	2(1-5)	2(1-5)	0.23
Non-calcified Plaque Score (NCPS)	1(0-3)	1(0-2)	1(0-2)	0.001
Calcified Plaque Score (CPS)	0(0-1)	0(0-2)	0(0-1)	0.059
Mixed Plaque Score (MPS)	0(0-1)	0(0-1)	0(0-1)	0.33

Adipose volume results are reported as mean (standard deviation) or percentage. Plaque scores are reported as median and interquartile range (IQR) or percentage.

*P-value comparing seropositive and seronegative values (unadjusted).

Table 4

Associations between Epicardial Adipose Tissue Volume and Presence of Coronary Artery Plaque (Plaque scores > 0 vs. 0)

	Coronary artery calcium N= 931 Prevalence=53%		Non-calcified plaque N= 706 Prevalence=60%		Calcified plaque N= 706 Prevalence=37%		Mixed plaque N= 706 Prevalence=34%		Any plaque N= 706 Prevalence=77%	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Model 1	1.04 (1.02,1.07)	0.003	1.06 (1.03,1.1)	<0.001	1.03 (1.002,1.07)	0.04	1.02 (0.99,1.06)	0.17	1.09 (1.04,1.14)	<0.001
Model 2	1.01 (0.98,1.04)	0.47	1.06 (1.02,1.1)	0.001	1.01 (0.97,1.04)	0.62	1.00 (0.97,1.04)	0.84	1.07 (1.02,1.12)	0.006
Model 3	1.01 (0.98,1.04)	0.55	1.07 (1.03,1.11)	0.001	1.00 (0.96,1.04)	0.98	1.01 (0.98,1.05)	0.49	1.06 (1.01,1.12)	0.02
Model 4	1.02 (0.98,1.06)	0.32	1.07 (1.02,1.11)	0.002	1.00 (0.96,1.04)	0.87	1.01 (0.97,1.05)	0.76	1.07 (1.01,1.13)	0.02

OR= odds ratio (per 10 units increase in Epicardial Adipose Tissue Volume); CI= confidence interval. Model 1- Adjusted for age, race and HIV serostatus; Model 2- Model 1 plus CAD risk factors; Model 3- Model 2 plus body mass index; Model 4- Model 2 plus abdominal visceral adipose volume. CAD risk factors include use of antihypertensive medications, systolic blood pressure (among those not on antihypertensive medications), use of diabetes medications, fasting glucose (among those not on diabetes medications), use of lipid medication use, triglyceride levels (among those not on lipid medications) and smoking (cumulative pack years)

AIDS. Author manuscript; available in PMC 2015 July 17.

Table 4A

Associations between Epicardial Adipose Tissue Volume and Presence of Coronary Artery Plaque (Plaque scores > 0 vs. 0) among HIV Seronegative

	Coronary artery calcium N= 352 Prevalence=53%		Non-calcified plaque N= 284 Prevalence=54%		Calcified plaque N= 284 Prevalence=40%		Mixed plaque N= 284 Prevalence = 32%		Any plaque N= 284 Prevalence=76%	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Model 1	1.05 (1,1.1)	0.065	1.06 (1.01,1.12)	0.025	1.01 (0.96,1.07)	0.67	1.02 (0.96,1.08)	0.51	1.07 (1,1.15)	0.059
Model 2	1.00 (0.95,1.05)	0.95	1.06 (1,1.13)	0.043	0.98 (0.92,1.04)	0.47	0.98 (0.92,1.05)	0.58	1.04 (0.96,1.12)	0.36
Model 3	0.97 (0.91,1.03)	0.34	1.09 (1.02,1.16)	0.015	0.96 (0.89,1.03)	0.22	0.99 (0.92,1.06)	0.72	1.04 (0.95,1.13)	0.43
Model 4	1.00 (0.94,1.07)	0.96	1.10 (1.02,1.18)	0.008	0.97 (0.9,1.04)	0.37	0.99 (0.92,1.06)	0.71	1.06 (0.97,1.17)	0.21

OR= odds ratio (per 10 units increase in Epicardial Adipose Tissue Volume); CI= confidence interval. Model 1- Adjusted for age and race; Model 2- Model 1 plus CAD risk factors; Model 3- Model 2 plus body mass index; Model 4- Model 2 plus abdominal visceral adipose volume. CAD risk factors include use of antihypertensive medications, systolic blood pressure (among those not on antihypertensive medications), use of diabetes medications, fasting glucose (among those not on diabetes medications), use of lipid medication use, triglyceride levels (among those not on lipid medications) and smoking (cumulative pack years)

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Table 4B

Associations between Epicardial Adipose Tissue Volume and Presence of Coronary Artery Plaque (Plaque scores > 0 vs. 0) among HIV Seropositive

	Coronary artery calcium N= 579 Prevalence=53%		Non-calcified plaque N= 422 Prevalence=64%		Calcified plaque N=422 Prevalence=34%		Mixed plaque N= 422 Prevalence=35%		Any plaque N=422 Prevalence=78%	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Model 1	1.04 (1.01,1.08)	0.02	1.06 (1.02,1.11)	0.005	1.05 (1.01,1.09)	0.015	1.02 (0.98,1.06)	0.27	1.10 (1.04,1.16)	0.001
Model 2	1.01 (0.98,1.05)	0.45	1.06 (1.01,1.10)	0.02	1.03 (0.99,1.07)	0.19	1.01 (0.97,1.05)	0.60	1.08 (1.02,1.15)	0.009
Model 3	1.03 (0.99,1.07)	0.20	1.05 (1.00,1.10)	0.054	1.03 (0.98,1.07)	0.29	1.02 (0.98,1.07)	0.31	1.07 (1.01,1.15)	0.03
Model 4	1.02 (0.98,1.07)	0.27	1.04 (0.99,1.10)	0.15	1.02 (0.97,1.08)	0.36	1.01 (0.97,1.07)	0.57	1.06 (0.98,1.14)	0.12

OR= odds ratio (per 10 units increase in Epicardial Adipose Tissue Volume); CI= confidence interval. Model 1- Adjusted for age and race; Model 2- Model 1 plus CAD risk factors; Model 3- Model 2 plus body mass index; Model 4- Model 2 plus abdominal visceral adipose volume. CAD risk factors include use of antihypertensive medications, systolic blood pressure (among those not on antihypertensive medications), use of diabetes medications, fasting glucose (among those not on diabetes medications), use of lipid medication use, triglyceride levels (among those not on lipid medications) and smoking (cumulative pack years)

AIDS. Author manuscript; available in PMC 2015 July 17.

Table 5

Associations between Epicardial Adipose Tissue Volume and Extent of Plaque among those with any Plaque Present (Plaque score > 0)

	Coronary Artery Calcium N= 93		Non-Calcified Plaque Score N= 423		Calcified Plaque Score N= 259		Mixed Plaque Score N= 239		Total Plaque Score N= 545	
	Effect estimate (SE)	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**
Model 1	0.048(0.013)	<0.001	0.011(0.006)	0.06	0.010(0.009)	0.26	0.005(0.009)	0.54	0.021(0.007)	0.001
Model 2	0.038(0.014)	0.006	0.005(0.006)	0.46	0.004(0.01)	0.67	0.001(0.009)	0.95	0.008(0.007)	0.23
Model 3	0.042(0.015)	0.005	0.007(0.007)	0.31	0.004(0.01)	0.73	-0.005(0.01)	0.66	0.010(0.008)	0.17
Model 4	0.048(0.017)	0.004	0.004(0.008)	0.56	0.007(0.011)	0.53	-0.007(0.011)	0.53	0.008(0.008)	0.31

Linear Regression of natural log transformed plaque scores among those with any plaque present; estimate represents log-plaque score change per 10 units increase in epicardial adipose tissue volume. SE= standard error; Model 1- Adjusted for age, race and HIV serostatus; Model 2- Model 1 plus CAD risk factors; Model 3- Model 2 plus body mass index; Model 4- Model 2 plus abdominal visceral adipose volume. CAD risk factors include systolic blood pressure, antihypertensive medication use, diabetes mellitus, fasting glucose, fasting triglyceride, use of lipid-lowering medications, and smoking (pack-years).

AIDS. Author manuscript; available in PMC 2015 July 17.

Table 5A

Associations between Epicardial Adipose Tissue Volume and Extent of Plaque among those with any Plaque Present (Plaque score > 0) among HIV Seronegative

	Coronary Artery Calcium N= 185		Non-Calcified Plaque Score N= 152		Calcified Plaque Score N= 114		Mixed Plaque Score N= 92		Total Plaque Score N= 215	
	Effect estimate (SE)	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**
Model 1	0.030(0.024)	0.21	0.030(0.010)	0.003	0.009(0.016)	0.59	0.004(0.018)	0.83	0.030(0.012)	0.01
Model 2	0.017(0.028)	0.53	0.016(0.010)	0.14	-0.005(0.018)	0.77	0.000(0.02)	0.98	0.012(0.012)	0.34
Model 3	0.014(0.030)	0.64	0.013(0.012)	0.29	0.000(0.019)	0.99	-0.024(0.022)	0.28	0.006(0.014)	0.66
Model 4	0.009(0.033)	0.78	0.008(0.012)	0.50	-0.002(0.020)	0.90	-0.011(0.023)	0.61	0.006(0.014)	0.67

Linear Regression of natural log transformed plaque scores among those with any plaque present; estimate represents log-plaque score change per 10 units increase in epicardial adipose tissue volume. SE= standard error; Model 1- Adjusted for age and race; Model 2- Model 1 plus CAD risk factors; Model 3- Model 2 plus body mass index; Model 4- Model 2 plus abdominal visceral adipose volume. CAD risk factors include systolic blood pressure, antihypertensive medication use, diabetes mellitus, fasting glucose, fasting triglyceride, use of lipid-lowering medications, and smoking (pack-years).

AIDS. Author manuscript; available in PMC 2015 July 17.

Table 5B

Associations between Epicardial Adipose Tissue Volume and Extent of Plaque among those with any Plaque Present (Plaque score > 0) among HIV Seropositive

	Coronary Artery Calcium N= 308		Non-Calcified Plaque Score N= 271		Calcified Plaque Score N= 145		Mixed Plaque Score N= 147		Total Plaque Score N= 330	
	Effect estimate (SE)	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**	**Effect estimate (SE)**	**p-value**
Model 1	0.056(0.016)	<0.001	0.002(0.008)	0.75	0.009(0.011)	0.400	0.005(0.010)	0.64	0.015(0.008)	0.055
Model 2	0.049(0.016)	0.002	-0.003(0.008)	0.66	0.005(0.012)	0.64	-0.002(0.011)	0.88	0.005(0.008)	0.54
Model 3	0.054(0.017)	0.002	0.002(0.009)	0.85	0.003(0.012)	0.81	0.004(0.012)	0.70	0.012(0.009)	0.20
Model 4	0.067(0.019)	<0.001	0.002(0.010)	0.87	0.010(0.014)	0.48	-0.007(0.013)	0.58	0.010(0.01)	0.32

Linear Regression of natural log transformed plaque scores among those with any plaque present; estimate represents log-plaque score change per 10 units increase in epicardial adipose tissue volume. SE= standard error; Model 1- Adjusted for age and race; Model 2- Model 1 plus CAD risk factors; Model 3- Model 2 plus body mass index; Model 4- Model 2 plus abdominal visceral adipose volume. CAD risk factors include systolic blood pressure, antihypertensive medication use, diabetes mellitus, fasting glucose, fasting triglyceride, use of lipid-lowering medications, and smoking (pack-years).

AIDS. Author manuscript; available in PMC 2015 July 17.