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Association of High-Sensitivity Troponin with Cardiac CT Angiography Evidence of Myocardial and Coronary Disease in a Primary Prevention Cohort of Men: Results from MACS

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Abstract

Background: High-sensitivity cardiac troponin (hs-cTn) elevations are associated with incident cardiovascular disease events in primary prevention samples. However, the mechanisms underlying this association remain unclear.

Methods: We studied 458 men without known cardiovascular disease who participated in the cardiovascular disease substudy of the Multicenter AIDS Cohort Study and had cardiac CT angiography. We used multivariable linear and logistic regression models to examine the cross-

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sectional associations between coronary artery stenosis, coronary artery plaque, indexed left ventricular mass (LVMi), and the outcome of hs-cTnI. We also evaluated the associations between HIV serostatus or use of highly active antiretroviral therapy (HAART) and hs-cTnI.

Results: The mean age was 54 years, 54% were white, and 61% were HIV infected. In multivariable-adjusted logistic models, comparing the highest quartile of LVMi with the lowest quartile, the odds ratio (OR) of hs-cTnI ≥75th percentile was 2.59 (95% CI, 1.20–5.75). There was no significant association between coronary stenosis severity or plaque type and hs-cTnI in linear models; however, in logistic regression models, coronary artery stenosis ≥70% (8% of sample) was marginally associated with a higher likelihood (OR, 2.75 [95% CI, 1.03, 7.27]) of having hs-cTnI ≥75th percentile. There were no associations between HIV serostatus or HAART use and hs-cTnI in either linear or logistic models.

Conclusion: Among primary prevention men with or at risk for HIV, hs-cTnI concentrations were strongly associated with LVMi but were not associated with HIV infection or treatment status or with coronary plaque type or stenosis until the extremes of severity (≥70% stenosis).

With the advent of highly active antiretroviral therapy (HAART)[10], the lifespan of HIV-infected persons is approaching that of the general population (1). As a result, HIV-infected persons increasingly are diagnosed with chronic age-related non-communicable diseases such as cardiovascular disease (CVD). By age 60, the cumulative CVD incidence has been estimated as 21% in men and 14% in women with HIV infection, compared with 13% and 9%, respectively, in the US general population (2, 3). HIV infection is associated with chronic inflammation, endothelial dysfunction, platelet activation, and coagulopathy, as well as a higher prevalence of CVD risk factors such as diabetes, hypertension, and dyslipidemia (2, 4). The use of HAART may in some circumstances further exacerbate dyslipidemia, diabetes, and endothelial dysfunction (4, 5) and increase the risk of CVD events (6). These findings all highlight the importance of recognizing the increased CVD risk among HIV-infected adults.

High-sensitivity cardiac troponin (hs-cTnI) has been identified as a novel circulating biomarker of subclinical myocardial damage in asymptomatic adults with no history of CVD (7, 8). Greater concentrations of hs-cTn are strongly and independently associated with future risk for heart failure, CVD death, and all-cause mortality in primary prevention cohorts (9–12). However, it is unclear whether hs-cTn elevation reflects primarily subclinical ischemia from occult coronary artery disease, structural heart disease (such as left ventricular hypertrophy, LVH), or a combination of both. Given the potential future use of hs-cTn as a biomarker of risk in the primary prevention setting (10) and as a surrogate marker for cardiovascular health (12), it is important to better understand the underlying mechanisms of hs-cTn elevation in adults without known CVD. Improved understanding of such mechanisms may be achieved by evaluating the relationship between hs-cTn and abnormalities detected by cardiac computed tomography angiography (CCTA). However,

[10]**Nonstandard abbreviations:** hs-cTn, high-sensitivity cardiac troponin; HAART, highly active antiretroviral treatment; CVD, cardiovascular disease; CCTA, cardiac computed tomography angiography; MACS, Multicenter AIDS Cohort Study; LVMi, indexed left ventricular mass; ART, antiretroviral therapy.

few if any rigorously conducted prospective cohorts of primary prevention adults without known CVD have high-quality CCTA data available.

In addition, although an association of HIV infection with increased subclinical coronary atherosclerosis as measured by cardiac CT has been previously shown (13, 14), to our knowledge, only 1 prior study has reported on the association between HIV and myocardial damage as measured by hs-cTn (13). Therefore, using cross-sectional data from a cohort of men with or at risk for HIV, but without known CVD, from the Multicenter AIDS Cohort Study (MACS), we sought to examine associations of hs-cTnI with left ventricular mass indexed to body surface area (LVMi) or with coronary anatomy (both measured by CCTA). As a secondary analysis, we assessed whether HIV serostatus modifies these associations.

MATERIALS AND METHODS

MACS is a prospective cohort study that enrolled HIV-infected and uninfected men who had sex with men (15). A total of 6972 participants were enrolled in Baltimore, Chicago, Pittsburgh, and Los Angeles during 3 periods: 1984–1985, 1987–1991, and 2001–2003. The MACS cardiovascular substudy included MACS participants who underwent CCTA imaging between January 2010 and June 2013 (n = 759) (14). Participants were between 40 and 70 years of age, weighed <300 pounds, and had no prior coronary artery bypass graft or valve surgery or history of coronary angioplasty. Participants were excluded if they had atrial fibrillation, intravenous contrast agent allergy, or chronic kidney disease with estimated glomerular filtration rate <60 mL/min/m^2 by the Modification of Diet in Renal Disease equation within 30 days of the CT scan. For the present analyses, we also excluded participants reporting any history of CVD events (n = 3) and those without available stored blood specimens for hs-cTnI testing (n = 298). Men remaining for analysis (n = 458) had cardiac CT imaging and hs-cTnI blood samples drawn on the same day. The study was approved by the institutional review boards of all participating sites and all participants provided informed consent.

MACS participants were seen every 6 months for standardized interviews, physical examination, and blood and urine collection. Baseline characteristics included in the current analysis were collected at the preceding MACS study visit closest to CT scanning. Body mass index was calculated as weight in kilograms divided by height in meters squared. Current smoking was self-reported. Hypertension was defined in MACS as blood pressure >140/90 mmHg or use of antihypertensive medications with a self-reported history of hypertension. Unfortunately, there was a significant amount of missing data (>25%) for this hypertension variable, so we used antihypertensive medication status as a surrogate for hypertension status given the former variable had no missing data. Diabetes was defined as fasting glucose ≥126 mg/dL, use of insulin, or use of oral hypoglycemic agents. Total cholesterol, HDL cholesterol, and triglycerides were measured after a 12-h fast. The Friedewald equation was used to estimate LDL cholesterol. HIV parameters collected included plasma HIV RNA concentrations, CD4 T-lymphocyte cell counts (cells/μL), type of antiretroviral therapy (ART) used, ART duration of exposure in years, and history of AIDS-defining malignancy or opportunistic infection.

Participants in the MACS-CVD study underwent a noncontrast CT to assess coronary artery calcium (CAC). If patients met eligibility criteria (see Data Supplement that accompanies the online version of this article at http://www.jalm.org/content/vol4/issue3) a contrast-enhanced CCTA was performed with a 64-slice multidetector scanner at 3 centers and a 320-slice CT scanner at the fourth center (Johns Hopkins Hospital) (16). A heart rate target of between 50 and 65 bpm was achieved with oral and/or intravenous β-blockers or calcium channel blockers as required. CT scans were read centrally at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. Coronary plaque was assessed and measured in each of the modified 15 coronary segments outlined by the American Heart Association (17). Plaque severity was subjectively graded: 0 = no plaque, 1 = mild plaque, 2 = moderate plaque, or 3 = severe plaque. For each reported segment of stenosis, the most narrowed diameter was graded between 0 and 4 according to percentage stenosis severity: 0 = no plaque/no stenosis, 1 = 1%–29%, 2 = 30%–49%, 3 = 50%–69%, or 4 = >70% stenoses. Each plaque was also assessed as calcified, noncalcified, or mixed (<50% area of plaque calcified). CAC scores were calculated with the method of Agatston (18). Measurements of the anteroinferior and septal-lateral diameters in the short-axis planes at the left ventricular midpapillary concentration, and 4-chamber long-axis left ventricular cavity lengths were obtained. These measurements were used to calculate left ventricular mass as previously described (19). We defined LVH as an LVMi ≥96 g/m^2 (not including papillary muscles) on the basis of previous studies (20).

Hs-cTnI was measured in 2017 from samples collected on the same day as CT imaging with the ARCHITECT STAT high-sensitivity troponin I assay (Abbott Laboratories) at the Johns Hopkins Hospital in Baltimore, MD. The 99^{th} percentile (upper reference limit) for this assay is 34.2 ng/L for men, 15.6 ng/L for women, and 26.2 ng/L for all healthy adults in the general population overall. The limit of detection for this assay is 1.2 ng/L with a coefficient of variation <10% at 4.7 ng/L.

Baseline characteristics were compared between participants according to quartiles of hs-cTnI with χ^2 for categorical and t-testing for continuous variables. Owing to a nonnormal distribution, we analyzed hs-cTnI concentrations as a $\log_e$-transformed continuous outcome variable and as a categorical outcome variable (≥75th percentile or <75th percentile of the overall sample distribution). We then tested the association of LVMi, coronary artery stenosis severity, and type of coronary artery plaque (calcified, noncalcified, and mixed) with the outcome of hs-cTnI by multivariable linear and logistic regressions. We tested LVMi as a continuous exposure variable, categorized in quartiles, and dichotomized as LVH vs no LVH. We subsequently evaluated if HIV serostatus and HAART use were associated with hs-cTnI concentrations. Finally, we determined whether the associations of LVMi, coronary artery stenosis and coronary artery plaque with hs-cTnI concentrations are modified by HIV serostatus (positive or negative).

We used 5 hierarchical models with progressive adjustment for covariates. Model 1 adjusted for age (years), race (white, African-American, Hispanic, or other), education, and study site (Baltimore, Chicago, Pittsburgh, Los Angeles); model 2 further adjusted for body mass index (kg/m^2), smoking status (never, former, current), smoking pack/year, and alcohol (never, low moderate, moderate heavy, hazardous use); model 3 further adjusted for systolic

BP (mmHg), antihypertensive medication use (yes/no), diabetes mellitus status (yes/no), estimated glomerular filtration rate (ml/min/m^2), concentrations of total cholesterol (mg/dL), HDL cholesterol (mg/dL), triglycerides (mg/dL), C-reactive protein (mg/L), and use of lipid-lowering medications (yes/no); model 4 also adjusted for HIV serostatus (positive or negative). Finally, model 5 adjusted for LVH (<96 g/m^2 or ≥96 g/m^2) in analyses with coronary artery stenosis as exposure and adjusted for coronary artery stenosis (<70% or ≥70%) for analyses with LVMi as exposure. We considered a 2-sided $P < 0.05$ as statistically significant.

RESULTS

Baseline characteristics of the study participants are presented in Table 1. The median hs-cTnI was 2.3 ng/L (interquartile range, 1.8–3.6 ng/L). Consistent with known percentile distributions for this assay, only 3 MACS participants (0.65%) had hs-cTnI >34.2 ng/L. Men with the uppermost hs-cTnI quartile had higher body mass index, higher systolic BP, and were more likely to be African-American or using diabetes medication than men in the lower quartiles. They were also more likely to have LVH and greater coronary artery stenosis severity on CCTA imaging, without significant differences in plaque composition. There were no differences in the crude proportion of men with HIV within each of the hs-cTnI quartiles. Fig. 1 in the online Data Supplement demonstrates the distribution of troponin I by age and type of coronary plaque.

When left ventricular mass was modeled as a categorical exposure by quartile, the continuous outcome variable of log-transformed hs-cTnI was higher in men in the fourth LVMi quartile than in those in the first LVMi quartile (adjusted β coefficient, 0.27; 95% CI, 0.08–0.47) (Table 2). No significant difference in hs-cTnI was seen between men with and without LVH, although the CIs were wide and the number of participants with LVH by this criterion was small (n = 9). In logistic regression models evaluating the full study sample, the OR for the categorical outcome of hs-cTnI ≥75th percentile was 2.59 (95% CI, 1.20–5.75) in the fourth LVMi quartile compared with the first quartile of LVMi (Fig. 1 and see Table 1 in the online Data Supplement). When stratified by HIV status, although the association between LVMi quartiles and odds of troponin ≥75th percentile (see Table 2 in the online Data Supplement) appeared stronger (OR, 6.22; 95% CI, 1.46–38.16, comparing fourth to first quartile of LVMi) in uninfected men than in HIV-infected men (OR, 1.63; 95% CI, 0.56–4.88), there was no evidence of statistical interaction for this comparison ($P = 0.38$).

We also examined the relationship between exposure categories of coronary stenosis severity and hs-cTnI as an outcome. In multivariable linear regression analyses with log-transformed troponin concentration as a continuous outcome variable, there was no significant association between severity of coronary artery stenoses and hs-cTnI (Tables 2 and 3). However, with hs-cTnI modeled as a binary outcome, the OR of having hs-cTnI ≥75th percentile was 2.75 (95% CI, 1.03–7.27) among men with coronary artery stenosis ≥70%, even after adjustment for baseline left ventricular hypertrophy (see Table 1 in the online Data Supplement). Prevalence of any coronary plaque or type of plaque were not associated with hs-cTnI concentration (Table 2). There was also no association between coronary

plaque and troponin concentrations when stratified by HIV serostatus (see Table 2 in the online Data Supplement).

Finally, we evaluated the relationship of HIV-specific variables, including HIV serostatus and HAART therapy, with hs-cTnI as the outcome. There were no significant differences in hs-cTnI concentrations between HIV-infected and uninfected men (Table 4 and see Table 3 in the online Data Supplement). Among HIV-infected participants, there were also no differences in hs-cTnI concentration between those receiving or not receiving HAART, and between HAART that did or did not include protease inhibitors.

DISCUSSION

The current study adds to our understanding of the association between abnormalities in cardiac anatomy, visualized with CCTA imaging, and high-sensitivity troponin concentrations in a well-characterized primary prevention cohort of HIV-infected and uninfected men. We also extend prior research by further assessing the relationship between HIV clinical parameters and hs-cTn concentrations. First, we demonstrate that higher LVMi is associated with subclinical myocardial damage, as indicated by hs-cTnI, among men without known CVD even after adjusting for severity of coronary artery disease. We were unable to adequately assess associations between LVH (as defined by a cutoff LVMi of ≥96 g/m^2) and hs-cTnI because there were very few cases with LVH in the MACS-CVD cohort. Abnormalities in coronary luminal anatomy appeared to be less convincingly associated with higher hs-cTnI concentrations in the primary prevention sample, although we did find a marginally significant association with hs-cTnI in the small subgroup (approximately 8%) with coronary artery stenoses ≥70%, which are typically considered clinically flow limiting (21). Second, presence of coronary plaque and plaque type among men with coronary atherosclerosis were not associated with hs-cTnI concentrations in our study, a result that appears to contradict prior findings (22). Third, we found no association between HIV serostatus and hs-cTnI concentrations, and although power may have been limited to detect weak associations, there was also no association with use and duration of HAART (or with ART drug class).

Troponin concentrations have been traditionally considered a diagnostic marker for acute myocardial infarction. The recent use of high-sensitivity, rather than standard, troponin assays has helped identify asymptomatic adults without known CVD at increased risk of future adverse CVD outcomes outside of the acute coronary syndrome setting. For example, in the Dallas Heart Study, after a median follow-up of 6.4 years, all-cause mortality was 1.9% in participants with undetectable hs-cTnT concentrations in comparison to 28.4% among those with hs-cTnT ≥14 ng/L(9). Similar findings of worse cardiovascular outcomes among persons with abnormal hs-cTn concentrations have been reported in multiple other cohorts of persons without known CVD (23).

However, the mechanisms underlying this association have been unclear. In the Dallas Heart Study, age, male sex, black race, left ventricular mass, and wall thickness by MRI were associated with detectable hs-cTnT, but no independent associations between hs-cTnT and history of myocardial infarction or angina, CAC, or left ventricular ejection fraction were

seen (9). However, to our knowledge, none of the primary prevention cohorts that have previously studied the determinants of hs-cTn abnormalities had CT angiography imaging information on coronary artery disease and stenosis severity. Hence, it remains incompletely understood whether the presence of higher high-sensitivity troponin concentrations in adults without known CVD is due to underlying coronary artery disease, to structural heart disease (e.g., higher LVMi reflecting severity of ventricular hypertrophy), or a mixture of both. Our results demonstrate that higher LVMi appears more consistently associated with higher hs-cTnI than subclinical coronary artery disease in primary prevention populations. Because individuals with the highest LVMi are particularly at risk of subclinical myocardial damage, persons without known CVD who are found to have an elevation in hs-cTn may benefit from investigation for structural heart disease (noting that obstructive coronary artery disease is also rare in this population). It is unclear if these individuals may also benefit from certain interventions such as more intensive BP reduction to reduce long-term risk (24).

In a small subgroup (<10%) of our sample with overtly asymptomatic although potentially flow-limiting coronary stenoses ≥70%, we also found marginally higher hs-cTnI concentrations and, as such, careful questioning regarding exercise capacity and chest pain status also appears indicated among adults without known CVD but with higher hs-cTn. Higher hs-cTn concentrations have previously been associated with subclinical coronary artery disease (as determined by CAC measured with noncontrast cardiac CT) in individuals without known coronary artery disease (25). However, this finding has been inconsistent, and CAC imaging does not provide any information regarding stenosis severity or burden of noncalcified atherosclerosis in the coronary bed (9).

Prior analyses evaluating associations between CCTA findings and hs-cTn concentrations have involved mainly small studies of patients with symptomatic coronary artery disease (typically stable chest pain) who were evaluated clinically by CCTA. In symptomatic patients, hs-cTn concentrations have been associated with coronary artery disease and severity of stenosis and, in intravascular ultrasound studies, have also been associated with total noncalcified plaque and the presence of vulnerable plaque features like positive remodeling or thin-cap fibroatheroma (26, 27). We add to prior work in this area by also testing the association between cardiac structure (in addition to coronary artery disease) and hs-cTn concentrations. Our study of men without known CVD would suggest that the associations between coronary disease and hs-cTn concentrations are weaker in persons without symptoms and that, in primary prevention, the main driver linking hs-cTn concentration abnormalities to adverse outcomes appears to be structural heart disease. This consideration is critical in our understanding of using hs-cTn concentration as a marker of myocardial health in primary prevention and as a possible surrogate outcome in clinical studies (28).

In addition to providing a unique opportunity to explore associations of cardiac structure and coronary anatomy with hs-cTnI concentrations among men without known CVD, our study also allowed for further assessment of the association between HIV clinical factors and hs-cTnI. HIV-infected persons have a greater prevalence of traditional CVD risk factors and an increased risk of CVD events (2, 3). Asymptomatic HIV-infected persons also have an increased prevalence of subclinical atherosclerosis with more calcified and, particularly

more noncalcified coronary artery plaque compared with HIV-uninfected individuals (14). In addition, HIV-infected persons appear to have a higher prevalence of vulnerable plaque that is associated with increased risk of CVD events (29).

Whether hs-cTn concentrations differ between HIV-infected and uninfected persons has been a subject of nascent investigation. Fitch et al. found an association between HIV infection and hs-cTn concentration abnormalities in a single center study of 225 asymptomatic participants, with an association apparent between hs-cTnT concentrations and coronary plaque presence among HIV-infected (n = 155) but not HIV-uninfected participants (n = 70) (13). However, the sample size was small with limited adjustment for potential confounders. In our larger, multicenter study with more rigorous adjustment for covariates, there was no association of hs-cTnI concentrations with any or type of coronary artery plaque among HIV-infected men. There were also no associations apparent between hs-cTnI concentrations and HIV serostatus, HAART presence or duration, or types of HAART. We were also able to add to the work of Fitch et al. by also reporting on LV mass, an informative addition given LVH is a known correlate of abnormal hs-cTnI concentrations in asymptomatic populations (9). The Fitch study and our study also differed in hs-Tn assays and control group characteristics. Larger studies, perhaps combining data from multiple cohorts, may provide more definitive data on the relationship between HIV infection and hs-cTn concentrations.

The strengths of our study include a diverse community-based population of men without known CVD, rigorous ascertainment of covariates, measurement of hs-cTnI concentrations at the exact same time CCTA images were acquired, and the inclusion of broad representation of both HIV-infected and uninfected male participants. However, there are some limitations. The limited number of cases may constrain the statistical power of our analyses to evaluate for interactions with hs-cTn concentrations, particularly regarding null findings for stenoses >50%, plaque type, and HIV exposures. MACS participants are men, and our findings may not be representative of women with or without HIV infection (2). Although approximately 40% of this sample was not HIV infected (but were at risk for HIV), our results may not be generalizable to all persons without known CVD in the community. Our sample consisted of a heterogeneous mixture of men with and without HIV. We do not see this as a major limitation, however, because most observational cohorts contain mixtures of demographic features (e.g., diabetics and nondiabetics) and we adjusted for HIV status in our models. Indeed, we are not aware of another large cohort of primary prevention adults who have both CCTA and hs-cTn data available and, hence, needed to leverage this particular cohort to probe the potential anatomical mechanisms underlying subclinical hs-cTn elevation in primary prevention adults. Troponin concentrations are known to be affected by renal function (30), and we cannot generalize our findings to those with atrial fibrillation and renal disease given that participants with atrial fibrillation and an estimated glomerular filtration rate <60 mL/min/1.73m^2 were excluded. Other limitations include the observational study design, which cannot rule out residual confounding as a factor in any associations reported.

In our primary prevention cohort of HIV-infected and uninfected men without known CVD, we found that asymptomatic individuals with higher hs-cTnI concentrations were more

likely to have increased LVMi and that hs-cTnI concentrations appeared to be less associated with coronary artery disease or plaque type, except in the small subgroup of approximately 8% of our sample with luminal stenosis ≥70%. These findings were apparent in both HIV-infected and uninfected men. The presence of HIV infection itself, or HIV disease clinical control status or HAART treatment, did not appear to be associated with hs-cTnI concentrations in our study. These findings corroborate prior knowledge that abnormalities in hs-cTn concentrations among adults without known CVD are more strongly tied to structural heart disease than to coronary artery stenosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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IMPACT STATEMENT

- These data inform our understanding of the mechanistic underpinnings of high-sensitivity troponin (hs-Tn) elevations among primary cardiovascular disease prevention adults. This finding is important because hs-Tn is prognostic in asymptomatic adults, but the reasons for hs-Tn elevation in this setting are poorly characterized.
- In asymptomatic men enrolled in a cardiac CT study, we measured hs-Tn in stored blood samples. We correlated cardiac CT findings (including coronary anatomy and cardiac structure) with hs-Tn.
- Our results demonstrate that increased left ventricular mass (which is common) is a more frequent driver of hs-Tn elevations in asymptomatic adults than occult occlusive coronary artery disease (which is uncommon), although both processes contribute.

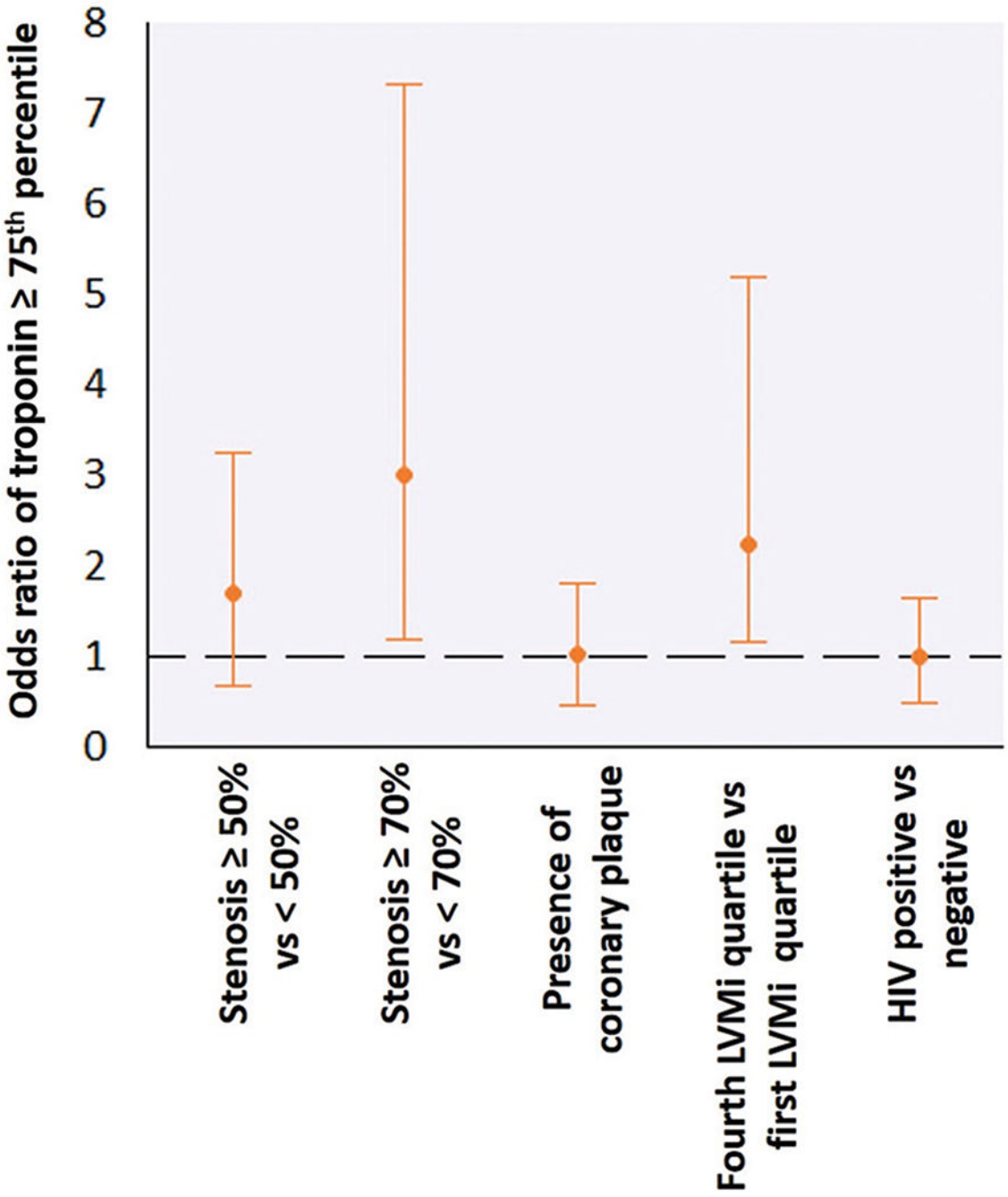

Fig. 1. ORs and 95% CIs for elevated troponin concentrations (high-sensitivity troponin I ≥ 75th percentile) according to degree of coronary artery stenosis, presence of coronary plaque (yes vs no), indexed left ventricular mass quartiles, and HIV status.

Multivariable adjustment for age, race, education, center, body mass index, smoking status, pack years smoked, alcohol intake, systolic blood pressure, antihypertensive medication use, diabetes status, eGFR, C-reactive protein, total cholesterol, HDL cholesterol, triglycerides, and use of lipid-lowering medications.

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Table 1.

Characteristics of participants by troponin concentrations at the visit closest to CT scan.[a]

		High-sensitivity troponin I (ng/L)				
Characteristic	**Overall**	**First quartile (0.2–1.7)**	**Second quartile (1.8–2.3)**	**Third quartile (2.4–3.6)**	**Fourth quartile (3.7–51.9)**	***P* value**
n	458	124	117	106	111	
Age, years	53.6 (7.1)	52.2 (6.3)	53.9 (7.7)	54.1 (7.2)	54.4 (7.2)	0.07
Race (%)						0.003
White	248 (54.1)	71 (57.3)	65 (55.6)	63 (59.4)	49 (44.1)	
African American	141 (30.8)	27 (21.8)	32 (27.4)	32 (30.2)	50 (45.0)	
Hispanic or other	69 (15.1)	26 (21.0)	20 (17.1)	11 (10.4)	12 (10.8)	
Education level						0.83
High school or less	103 (22.5)	29 (23.4)	20 (17.1)	25 (23.6)	29 (26.1)	
At least 1 year of college	128 (27.9)	39 (31.5)	36 (30.8)	27 (25.5)	26 (23.4)	
Undergraduate degree	93 (20.3)	23 (18.5)	24 (20.5)	23 (21.7)	23 (20.7)	
Graduate degree	134 (29.3)	33 (26.6)	37 (31.6)	31 (29.2)	33 (29.7)	
Study sites						0.04
Baltimore	192 (41.9)	47 (37.9)	42 (35.9)	52 (49.1)	51 (45.9)	
Chicago	29 (6.3)	5 (4.0)	4 (3.4)	9 (8.5)	11 (9.9)	
Pittsburgh	32 (7.0)	6 (4.8)	10 (8.5)	8 (7.5)	8 (7.2)	
Los Angeles	205 (44.8)	66 (53.2)	61 (52.1)	37 (34.9)	41 (36.9)	
Tobacco use						0.24
Never	111 (24.2)	37 (29.8)	31 (26.5)	21 (19.8)	22 (19.8)	

Characteristic	Overall	High-sensitivity troponin I (ng/L) First quartile (0.2–1.7)	Second quartile (1.8–2.3)	Third quartile (2.4–3.6)	Fourth quartile (3.7–51.9)	*P* value
Former	230 (50.2)	58 (46.8)	62 (53.0)	57 (53.8)	53 (47.7)	
Current	117 (25.5)	29 (23.4)	24 (20.5)	28 (26.4)	36 (32.4)	
Cumulative smoking pack-years	3.8 [0.0–20.0]	0.7 [0.0–14.9]	3.7 [0.0–23.9]	4.1 [0.0–19.7]	5.4 [0.0–21.2]	0.17
Alcohol[b]						0.45
Never	101 (22.1)	30 (24.2)	18 (15.4)	26 (24.5)	27 (24.3)	
Low moderate	282 (61.6)	73 (58.9)	74 (63.2)	65 (61.3)	70 (63.1)	
Moderate heavy	52 (11.4)	12 (9.7)	19 (16.2)	11 (10.4)	10 (9.0)	
Hazardous use	23 (5.0)	9 (7.3)	6 (5.1)	4 (3.8)	4 (3.6)	
Number of alcohol drinks/week	0.4 [0.2–3.5]	0.4 [0.2–1.5]	1.5 [0.2–3.5]	0.3 [0.2–1.5]	0.3 [0.2–1.5]	0.17
Body mass index (kg/m^2)	26.6 (4.5)	25.1 (3.3)	26.6 (4.7)	27.2 (4.6)	27.5 (5.0)	0.001
Systolic blood pressure, mmHg	126 (15)	121 (12)	123 (13)	129 (16)	130 (15)	0.001
Total cholesterol, mg/dL	189.5 (37.9)	186.8 (40.1)	192.1 (35.9)	190.6 (39.6)	188.6 (36.1)	0.72
HDL-C, mg/dL[c]	49.6 (15.1)	51.5 (16.0)	48.7 (13.5)	48.0 (13.0)	50.1 (17.2)	0.30
LDL-C, mg/dL	112.0 (34.7)	108.3 (36.3)	114.7 (32.9)	114.2 (36.8)	111.3 (32.8)	0.47
Triglyceride level, mg/dL	119 [85–173]	122 [83–170]	125 [84–183]	119 [92–171]	108 [82–171]	0.75
Statin use (%)	136 (31.9)	37 (31.6)	34 (31.5)	29 (30.2)	36 (34.3)	0.94
C-reactive protein, mg/L	1.1 [0.6–2.4]	0.9 [0.5–1.7]	1.5 [0.8–2.6]	1.0 [0.5–2.0]	1.2 [0.5–3.0]	0.002
Hypertension medication use (%)	146 (31.9)	31 (25.0)	35 (29.9)	40 (37.7)	40 (36.0)	0.14
Diabetes status (%)	40 (9.2)	10 (8.1)	5 (4.5)	13 (13.3)	12 (11.7)	0.13

Characteristic	Overall	High-sensitivity troponin I (ng/L) First quartile (0.2–1.7)	Second quartile (1.8–2.3)	Third quartile (2.4–3.6)	Fourth quartile (3.7–51.9)	*P* value
eGFR (mL/min/m^2)	92.3 (15.2)	93.3 (14.6)	91.4 (15.3)	93.0 (15.4)	91.7 (15.8)	0.72
Lipid medications (%)	155 (34.4)	40 (32.8)	40 (34.8)	34 (33.0)	41 (36.9)	0.91
HIV infected (%)	278 (60.7)	77 (62.1)	71 (60.7)	66 (62.3)	64 (57.7)	0.89
Persons with detectable HIV RNA[d]	224 (82.4)	59 (79.7)	64 (91.4)	51 (79.7)	50 (78.1)	0.14
CD4$^+$ T-cell count nadir (cells/mm^3)	334.8 (202.3)	346.9 (194.1)	296.9 (197.8)	365.8 (209.0)	331.0 (207.8)	0.24
HAART exposure (%)						0.95
Protease inhibitor use	57 (12.4)	12 (9.7)	14 (12.0)	14 (13.2)	17 (15.3)	
NNRTI use	36 (7.9)	10 (8.1)	9 (7.7)	9 (8.5)	8 (7.2)	
Other	185 (40.4)	55 (44.4)	48 (41.0)	43 (40.6)	39 (35.1)	
Obstructive Coronary Stenosis ≥ 70%	34 (7.6)	4 (3.3)	11 (9.6)	3 (2.9)	16 (14.8)	0.002
Coronary artery disease						0.02
Stenosis <30%	290 (63.3)	90 (72.6)	66 (56.4)	70 (66.0)	64 (57.7)	
30% ≤ Stenosis < 50%	95 (20.7)	21 (16.9)	28 (23.9)	25 (23.6)	21 (18.9)	
Stenosis ≥ 50%	73 (15.9)	13 (10.5)	23 (19.7)	11 (10.4)	26 (23.4)	
Coronary plaque prevalence						
Any coronary plaque	343 (74.9)	89 (71.8)	86 (73.5)	80 (75.5)	88 (79.3)	0.59
Noncalcified plaque	272 (59.4)	67 (54.0)	71 (60.7)	69 (65.1)	65 (58.6)	0.39
Mixed plaque	165 (36.0)	42 (33.9)	42 (35.9)	33 (31.0)	48 (43.2)	0.28
Calcified plaque	172 (37.6)	41 (33.1)	43 (36.8)	38 (35.8)	50 (45.0)	0.27

Characteristic	Overall	High-sensitivity troponin I (ng/L) First quartile (0.2–1.7)	Second quartile (1.8–2.3)	Third quartile (2.4–3.6)	Fourth quartile (3.7–51.9)	*P* value
LVMi (g/m^2)	56.9 (14.6)	53.4 (12.9)	54.4 (11.7)	59.2 (15.8)	61.7 (16.4)	0.001
Left ventricular hypertrophy[e] (%)	9 (2.0)	1 (0.8)	0 (0)	5 (5.0)	3 (2.8)	0.05

[a] Data are mean (SD), median [interquartile range], or number (percentage).

[b] Low moderate, 1–2 drinks/day or 3–4 drinks/day for no more than once a month; moderate heavy, 3–4 drinks/day for more than once a month or ≥5 drinks/day for less than once a month; hazardous use, ≥5 drinks/day for at least once a month.

[c] HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor.

[d] Detectable considered ≥ 50 copies/mL, proportion is of HIV infected participants.

[e] Left ventricular hypertrophy defined as ≥ 96g/m^2.

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Table 2.

The association of log-transformed high-sensitivity troponin I concentrations with coronary artery stenosis and indexed left ventricular mass.[a]

	N	Model 1[b]	Model 2[C]	Model 3[d]	Model 4[e]	Model 5[f]
Stenosis category 1						
Stenosis < 50%	376	Ref	Ref	Ref	Ref	Ref
Stenosis ≥ 50%	73	0.12 (−0.05, 0.29)	0.11 (−0.06, 0.28)	0.09 (−0.08, 0.27)	0.09 (−0.09, 0.27)	0.06 (−0.12, 0.24)
Stenosis category 2						
Stenosis < 70%	414	Ref	Ref	Ref	Ref	Ref
Stenosis ≥ 70%	34	0.19 (−0.04, 0.42)	0.19 (−0.04, 0.42)	0.19 (−0.06, 0.44)	0.19 (−0.06, 0.44)	0.18 (−0.09, 0.44)
Stenosis category 3						
Stenosis < 30%	290	Ref	Ref	Ref	Ref	Ref
30% ≤ Stenosis < 50%	95	−0.03 (−0.18, 0.13)	−0.04 (−0.19, 0.12)	−0.01 (−0.17, 0.15)	−0.02 (−0.18, 0.14)	−0.03 (−0.20, 0.13)
Stenosis ≥ 50%	73	0.11 (−0.06, 0.29)	0.10 (−0.07, 0.27)	0.09 (−0.09, 0.28)	0.09 (−0.10, 0.27)	0.05 (−0.14, 0.24)
Presence of any coronary plaque						
No	115	Ref	Ref	Ref	Ref	
Yes	343	0.04(−0.11, 0.18)	−0.01 (−0.16, 0.14)	−0.05 (−0.21, 0.10)	−0.06 (−0.22, 0.09)	
Presence of noncalcified plaque						
No	186	Ref	Ref	Ref	Ref	
Yes	272	0.02 (−0.10, 0.15)	0.00 (−0.13, 0.12)	−0.03 (−0.16, 0.10)	−0.04 (−0.17, 0.09)	
Presence of mixed plaque						
No	293	Ref	Ref	Ref	Ref	
Yes	165	0.03 (−0.11, 0.16)	0.02 (−0.11, 0.15)	0.00 (−0.13, 0.14)	0.00 (−0.14, 0.14)	
Presence of calcified plaque						
No	286	Ref	Ref	Ref	Ref	
Yes	172	0.07 (−0.06, 0.21)	0.05 (−0.08, 0.18)	0.05 (−0.09, 0.19)	0.05 (−0.09, 0.19)	
Structural heart disease						
Indexed LV[g] mass < 96 g/m^2	432	Ref	Ref	Ref		
Indexed LV mass ≥ 96 g/m^2	9	0.39 (−0.05, 0.83)	0.39 (−0.05, 0.82)	0.28 (−0.18, 0.74)	0.27 (−0.19, 0.73)	0.32 (−0.17, 0.81)
Continuous indexed LV mass	441	0.01 (0.01, 0.02)	0.01 (0.01, 0.01)	0.01 (0.00, 0.01)	0.01 (0.00, 0.01)	0.01 (0.00, 0.01)

	N	Model 1[b]	Model 2[C]	Model 3[d]	Model 4[e]	Model 5[f]
Indexed LV mass[h]						
Quartile 1 (23.7, 46.7)	108	**Ref**	**Ref**	**Ref**	**Ref**	**Ref**
Quartile 2 (46.7, 54.4)	110	0.08 (−0.10, 0.26)	0.08 (−0.09, 0.26)	0.04 (−0.14, 0.23)	0.04 (−0.14, 0.22)	0.03 (−0.16, 0.22)
Quartile 3 (54.4, 63.6)	112	0.28 (0.10, 0.45)	0.26 (0.08, 0.44)	0.22 (0.03, 0.40)	0.22 (0.03, 0.40)	0.22 (0.03, 0.41)
Quartile 4 (63.6, 120.4)	111	0.40 (0.22, 0.58)	0.37 (0.20, 0.55)	0.27 (0.08, 0.47)	0.27 (0.08, 0.46)	0.27 (0.08, 0.47)

[a]Assessed by multivariable linear regression with presentation of β coefficients.

[b]Model 1 is adjusted for age, race, education, and center.

[c]Model 2 is further adjusted for body mass index, smoking status, smoking pack/year, and alcohol intake.

[d]Model 3 is further adjusted for systolic blood pressure, antihypertensive medication use, diabetes status, eGFR, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and use of lipid-lowering medications.

[e]Model 4 is further adjusted for HIV infection status.

[f]Model 5 shows stenosis further adjusted for LV hypertrophy (indexed LV mass ≥ 96 g/m^2), and structural heart models further adjusted for stenosis (<70% or ≥70%).

[g]LV, left ventricular.

[h]Quartile parameters indicated in parenthesis in g/m^2.

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Table 3.

The association of log-transformed high-sensitivity troponin I concentrations with coronary artery stenosis and indexed left ventricular mass by HIV serostatus.[a]

	HIV infected				HIV uninfected		
	N	Model 1[b]	Model 2[C]	Model 3[d]	N	Model 1	Model 2	Model 3
Stenosis categories 1								
Stenosis < 50%	229	Ref	Ref	Ref	147	Ref	Ref	Ref
Stenosis ≥ 50%	42	0.12 (−0.08, 0.33)	0.13 (−0.07, 0.34)	0.11 (−0.10, 0.33)	31	0.10 (−0.19, 0.40)	0.01 (−0.29, 0.32)	0.00 (−0.34, 0.34)
Stenosis categories 2								
Stenosis < 70%	252	Ref	Ref	Ref	162	Ref	Ref	Ref
Stenosis ≥ 70%	18	0.27[e] (−0.03, 0.57)	0.29[e](−0.01, 0.58)	0.34 (0.03, 0.66)	16	0.11 (−0.27, 0.49)	0.02 (−0.36, 0.40)	0.02 (−0.41, 0.46)
Stenosis categories 2								
Stenosis < 30%	168	Ref	Ref	Ref	122	Ref	Ref	Ref
30% ≤ Stenosis < 50%	68	0.01 (−0.18, 0.19)	0.02 (−0.16, 0.19)	0.05 (−0.13, 0.24)	27	0.01 (−0.30, 0.32)	−0.07 (−0.39, 0.24)	0.00 (−0.34, 0.34)
Stenosis ≥ 50%	42	0.13 (−0.09, 0.34)	0.14 (−0.07, 0.35)	0.13 (−0.09, 0.36)	31	0.11 (−0.19, 0.41)	0.001 (−0.31, 0.31)	0.01 (−0.34, 0.36)
Presence of any coronary plaque								
No	64	Ref	Ref	Ref	51	Ref	Ref	Ref
Yes	214	0.06 (−0.12, 0.25)	0.01 (−0.17, 0.19)	−0.02 (−0.20, 0.17)	129	0.07 (−0.18, 0.33)	−0.01 (−0.27, 0.26)	−0.03 (−0.31, 0.25)
Presence of noncalcified plaque								
No	102	Ref	Ref	Ref	84	Ref	Ref	Ref
Yes	176	0.03 (−0.13, 0.19)	−0.04 (−0.20, 0.11)	−0.06 (−0.22, 0.10)	96	0.08 (−0.14, 0.29)	0.07 (−0.14, 0.29)	0.08 (−0.16, 0.32)
Presence of mixed plaque								

	HIV infected			HIV uninfected			
	N	Model 1[b]	Model 2[C]	Model 3[d]	N	Model 1	Model 2	Model 3
No	179	Ref	Ref	Ref	114	Ref	Ref	Ref
Yes	99	−0.02 (−0.18, 0.13)	0.00 (−0.16, 0.15)	0.02 (−0.14, 0.18)	66	0.15 (−0.09, 0.39)	0.12 (−0.12, 0.36)	−0.01 (−0.29, 0.26)
Presence of calcified plaque								
No	181	Ref	Ref	Ref	105	Ref	Ref	Ref
Yes	97	0.04 (−0.12, 0.19)	0.02 (−0.14, 0.18)	0.01 (−0.16, 0.17)	75	0.14 (−0.11, 0.39)	0.09 (−0.16, 0.34)	0.11 (−0.17, 0.38)
Structural heart disease								
LV[f] mass < 96 g/m^2	259	Ref	Ref	Ref	173	Ref	Ref	Ref
LV mass ≥ 96 g/m^2	8	0.42 (−0.01, 0.86)	0.42 (0.00, 0.84)	0.30 (−0.15, 0.76)	1	−0.30 (−1.78, 1.18)	−0.38 (−1.87, 1.10)	−0.24 (−1.73, 1.25)
Continuous indexed LV mass	441	0.01 (0.00, 0.01)	0.01 (0.00, 0.01)	0.01 (0.00, 0.01)	174	0.02 (0.01, 0.03)	0.02 (0.01, 0.02)	0.01 (0.01, 0.02)
Indexed LV mass[e]								
Quartile 1 [23.7, 46.7]	65	Ref	Ref	Ref	43	Ref	Ref	Ref
Quartile 2 [46.7, 54.4]	71	0.03 (−0.19, 0.24)	0.04 (−0.17, 0.25)	0.00 (−0.22, 0.21)	39	0.19 (−0.13, 0.50)	0.16 (−0.16, 0.48)	0.19 (−0.17, 0.54)
Quartile 3 [54.4, 63.6]	62	0.24 (0.02, 0.47)	0.23 (0.01, 0.46)	0.18 (−0.05, 0.41)	50	0.33 (0.03, 0.63)	0.29 (−0.01, 0.59)	0.33 (0.00, 0.65)
Quartile 4 [63.6, 120.4]	69	0.30 (0.09, 0.52)	0.27 (0.06, 0.48)	0.21 (−0.02, 0.44)	42	0.56 (0.24, 0.87)	0.47 (0.15, 0.80)	0.38 (0.02, 0.74)

[a] Assessed by multivariable linear regression with presentation of β coefficients.

[b] Model 1 is adjusted for age, race, education, and center.

[c] Model 2 is further adjusted for body mass index, smoking status, smoking pack/year, and alcohol intake.

[d] Model 3 is further adjusted for systolic blood pressure, antihypertensive medication use, diabetes status, eGFR, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and use of lipid-lowering medications.

[e] Quartile parameters indicated in parenthesis in g/m2.

[f] LV, left ventricular.

Table 4.

The association of log-transformed high-sensitivity troponin I concentrations with HIV treatment variables.[a]

	N	Model 1[b]	Model 2[C]	Model 3[d]
HIV infected vs HIV uninfected	458	−0.02 (−0.15, 0.11)	0.02 (−0.11, 0.15)	0.07 (−0.08, 0.21)
HAART[e] vs No HAART in HIV-infected men	278	−0.12 (−0.29, 0.06)	−0.09 (−0.26, 0.08)	−0.07 (−0.25, 0.11)[f]
HAART				
HIV uninfected	180	Ref	Ref	Ref
No HAART therapy in HIV infected	179	−0.06 (−0.20, 0.08)	−0.01 (−0.15, 0.13)	0.03 (−0.11, 0.18)
Nonprotease inhibitor HAART	57	0.09 (−0.12, 0.30)	0.09 (−0.12, 0.31)	0.13 (−0.09, 0.35)
Protease inhibitor HAART	42	0.03 (−0.21, 0.27)	0.10 (−0.14, 0.33)	0.17 (−0.08, 0.41)
Per 1-year increase in HAART duration	278	0.02 (−0.04, 0.08)	0.01 (−0.05, 0.07)	0.01 (−0.06, 0.08)[f]

[a] Assessed by multivariable linear regression with presentation of β coefficients.

[b] Model 1 is adjusted for age, race, education, and center.

[c] Model 2 is further adjusted for body mass index, smoking status, smoking pack/year, and alcohol intake.

[d] Model 3 is further adjusted for systolic blood press, antihypertensive medication use, diabetes status, eGFR, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and use of lipid-lowering medications.

[e] HAART, high active antiretroviral therapy.

[f] Further adjusted for $CD4^+$ (on HAART).