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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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Short title: High sensitivity troponin and cardiac CT findings

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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 sub-study of the Multicenter AIDS Cohort Study and had cardiac CT angiography. We used multivariable linear and logistic regression models to examine the cross-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 of hs-cTnI ≥ 75th percentile was 2.36 (95% confidence interval 1.11 to 5.13). 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 associated with a higher likelihood (OR 3.08) 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 levels 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).

Abstract word count: 248

Key words: high-sensitivity troponin; coronary disease; left ventricular hypertrophy; cardiac computed tomography

Abbreviations: HAART = highly active antiretroviral treatment; LVMi = indexed left ventricular mass; hs-cTn = high-sensitivity cardiac troponin; CVD = cardiovascular disease

Introduction:

With the advent of highly active antiretroviral therapy (HAART), 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 prior history of CVD.[7,8] Greater levels 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 using cardiac computed tomography angiography (CCTA). However, few if any rigorously conducted prospective cohorts of primary prevention adults without known CVD have high-quality CCTA data available.

In addition, while an association of HIV infection with increased subclinical coronary atherosclerosis as measured using cardiac CT has been previously shown,[13,14] much less is known about the association between HIV and myocardial damage as measured by hs-cTn.[13] Therefore, using cross-sectional data from a cohort of men without known CVD, with or at risk for HIV, 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.

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 three time periods: 1984 to 1985, 1987 to 1991, and 2001 to 2003. The MACS cardiovascular sub-study included MACS participants who underwent CCTA imaging between January 2010 and June 2013 (n= 759).[14] Participants were between 40 to 70 years of age, weighed less than 300 pounds, and had no prior coronary artery bypass graft or valve surgery, or prior history of coronary angioplasty. Participants were excluded if they had atrial fibrillation, intravenous contrast allergy, or chronic kidney disease with estimated glomerular filtration rate < 60 ml/min/m^2 using 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.

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 as blood pressure > 140/90 mmHg or use of antihypertensive medications with a self-reported history of hypertension. Diabetes was defined as fasting glucose ≥ 126 mg/dL or use of

insulin or oral hypoglycemic agents. Total and high-density lipoprotein cholesterol, and triglycerides were measured after a 12 hour fast. The Friedewald equation was used to estimate low-density lipoprotein cholesterol. HIV parameters collected included plasma HIV RNA levels, CD4 T-lymphocyte cell counts (cells/μL), type of antiretroviral therapy (ART) used and ART duration of exposure in years, as well as history of AIDS-defining malignancy or opportunistic infection.

Participants in the MACS-CVD study underwent a non-contrast CT to assess coronary artery calcium (CAC). If patients met eligibility criteria (see Online Supplement) a contrast-enhanced CCTA was performed using a 64-slice multi-detector scanner at three centers and a 320-slice CT scanner at the fourth center (Johns Hopkins Hospital).[16] A heart rate target of between 50-65 bpm was achieved using oral and/or intravenous beta-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 to 4 according to percent stenosis severity: 0 = no plaque/no stenosis, 1 = 1-29%, 2 = 30-49%, 3 = 50-69%, or 4 = greater than 70% stenoses. Each plaque was also

assessed as calcified, noncalcified, or mixed (less than 50% area of plaque calcified). CAC scores were calculated using the method of Agatston.[18] Measurements of the anteroinferior and septal-lateral diameters in the short-axis planes at the left ventricular mid-papillary level, and four-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), based on previous studies.[20]

Hs-cTnI was measured from samples collected on the same day as CT imaging using the ARCHITECT STAT high sensitive Troponin I assay (Abbott Laboratories', Abbott Park, IL). The 99th% (upper reference limit) for this assay is 34.2 ng/L for males, 15.6 ng/L for females and 26.2 ng/L for all healthy adults in the general population overall. The limit of detection (LOD) 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 using chi-square for categorical and t-testing for continuous variables. Due to a non-normal distribution, we analyzed hs-cTnI levels 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, non-calcified and mixed) with the outcome of hs-cTnI using 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 levels. Finally, we determined whether the associations of LVMi, coronary artery stenosis and coronary artery plaque with hs-cTnI levels are modified by HIV serostatus (positive or negative).

We used hierarchical 4 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 BMI (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), anti-hypertensive medication use (yes/no), diabetes medication use (yes/no), levels of total cholesterol (mg/dL), high-density lipoprotein 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 $\geq 70\%$) 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**. 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.

When left ventricular mass was modeled as a categorical exposure by quartile, the outcome of log-transformed hs-cTnI was higher in the fourth LVMi quartile compared to men in the first LVMi quartile (adjusted beta-coefficient 0.30, 95% confidence interval [CI] 0.11 to 0.49) (**Table 2**). No significant difference in hs-cTnI was seen between men with and without LVH, although the confidence intervals were wide and the number of participants with LVH by this criterion was small (n=9). In logistic regression models, the odds ratio for the outcome of hs-cTnI ≥ 75th percentile was 2.36 (95% CI 1.11 to 5.13) in the fourth LVMi quartile compared with the first quartile (**Figure 1, Supplemental Table 1**). Although the association between LVMi quartiles and odds of troponin ≥ 75th percentile (**Supplemental Table 2**) appeared stronger (OR 6.28; 95% CI 1.52 to 31.04, comparing 4th to 1st quartile of LVMi) in HIV-uninfected men than in

HIV-infected men (OR 1.33; 95% CI 0.47 to 3.78), there was no evidence of statistical interaction for this comparison (p=0.36).

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 level as a continuous outcome variable, there was no significant association between hs-cTnI and severity of coronary artery stenoses (**Tables 2 and 3**). However, with hs-cTnI modeled as a binary outcome, the odds ratio of having hs-cTnI ≥75th percentile was 3.08 (95% CI 1.23 to 7.74) among men with coronary artery stenosis ≥70% even after adjustment for baseline left ventricular hypertrophy (**Supplemental Table 1**). Hs-cTnI levels were not associated with prevalence of any coronary plaque or type of plaque (**Table 2**). There was also no association between troponin levels with coronary plaque when stratified by HIV serostatus (**Supplemental Table 2**).

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 levels between HIV-infected and uninfected men (**Table 4** and **Supplementary Table 3**). Among HIV-infected participants, there were also no differences in hs-cTnI level 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 using CCTA imaging, and high-sensitivity troponin levels 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 levels. 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 LVM of ≥ 96 g/m^2) and since there were very few cases with LVH in the MACS-CVD cohort. Abnormalities in coronary luminal anatomy appeared to be less convincingly associated with elevated hs-cTnI levels in the primary prevention sample, though we did find an association with hs-cTnI in the small subgroup (~8%) with coronary artery stenoses ≥ 70%, which are typically considered clinically flow limiting.[21] Second, presence of coronary plaque or plaque type among men with coronary atherosclerosis were not associated with hs-cTnI levels in our study, a result that appears to contradict prior findings.[22] Third, we found no association between HIV serostatus and hs-cTnI levels 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 levels have been traditionally considered a diagnostic marker for acute myocardial infarction. The recent use of high-sensitivity, over 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 levels 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 levels 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 prior history of myocardial infarction or angina, coronary artery calcium, 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 poorly understood whether the presence of elevated high-sensitivity troponin levels 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 mix of both. Our results demonstrate that higher LVMi appears more

consistently associated with elevated hs-cTnI in populations 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 CAD 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 though potentially flow limiting coronary stenoses ≥70%, we also found elevated hs-cTnI levels and, as such, careful questioning regarding exercise capacity and chest pain status also appears indicated among adults without known CVD with elevated hs-cTn. Elevated hs-cTn levels have previously been associated with subclinical CAD (as determined by coronary artery calcium measured using non-contrast cardiac CT) in individuals without known coronary artery disease.[25] However this finding has been inconsistent and coronary artery calcium imaging does not any provide information regarding stenosis severity or burden of non-calcified atherosclerosis in the coronary bed.[9]

To our knowledge, this is the first study to examine the association between coronary artery disease measured using a more sensitive imaging modality, contrast-enhanced CCTA, and hs-cTn levels among adults without known CVD. Prior analyses evaluating associations between CCTA findings

and hs-cTn levels have involved mainly small studies of patients with symptomatic coronary artery disease (typically stable chest pain) who were evaluated clinically using CCTA. In symptomatic patients, hs-cTn levels have been associated with coronary artery disease and severity of stenosis, and, using intravascular ultrasound, have also been associated with total non-calcified plaque and the presence of vulnerable plaque features like positive remodeling or thin-cap fibroatheroma.[26,27] Our study of men without known CVD would suggest that the associations between coronary disease and hs-cTn levels are weaker in persons without symptoms and that, in primary prevention, the main driver linking hs-cTn level abnormalities to adverse outcomes appears to be structural heart disease. This consideration is critical in our understanding of using hs-cTn level 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 levels 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 non-calcified 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]

Previously, it has been unclear if hs-cTn levels may differ between HIV-infected and uninfected persons. Fitch et al. found an association between HIV infection and hs-cTn level abnormalities in a single center study of 225 asymptomatic participants, with an association apparent between hs-cTnT levels 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, multi-center study with more rigorous adjustment for covariates, there was no association of hs-cTnI levels with any or type of coronary artery plaque among HIV-infected men. There were also no associations apparent between hs-cTnI levels and HIV serostatus, HAART presence/duration, or types of HAART. The Fitch study and our study also differed in hsTn 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 levels.

The strengths of our study include a diverse community-based population of men without known CVD, rigorous ascertainment of covariates, measurement of hs-cTnI levels at the same time as 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 levels, 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] While ~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. Further, our sample consisted of a heterogenous mix of men with and without HIV. We do not see this as a major limitation; however, as most observational cohorts contain mixes of demographic features (e.g. diabetics and non-diabetics) 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 levels are known to be affected by renal function,[30] and we cannot generalize our findings to those with renal disease given participants with 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 cohort of HIV-infected and uninfected men without known CVD, we found that asymptomatic individuals with elevated hs-cTnI levels were more likely to have increased LVMi and that hs-cTnI levels appeared less associated with coronary artery disease or plaque-type, except in the small

subgroup of approximately 8% of men with luminal stenosis ≥70%. These findings were apparent in both HIV-infected and uninfected men. The presence of HIV infection itself, nor HIV disease clinical control status nor HAART treatment, did not appear to be associated with hs-cTnI levels in our study. These findings corroborate prior knowledge that abnormalities in hs-cTn levels among adults without known CVD are more strongly tied to structural heart disease than to coronary artery stenosis.

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Disclosures

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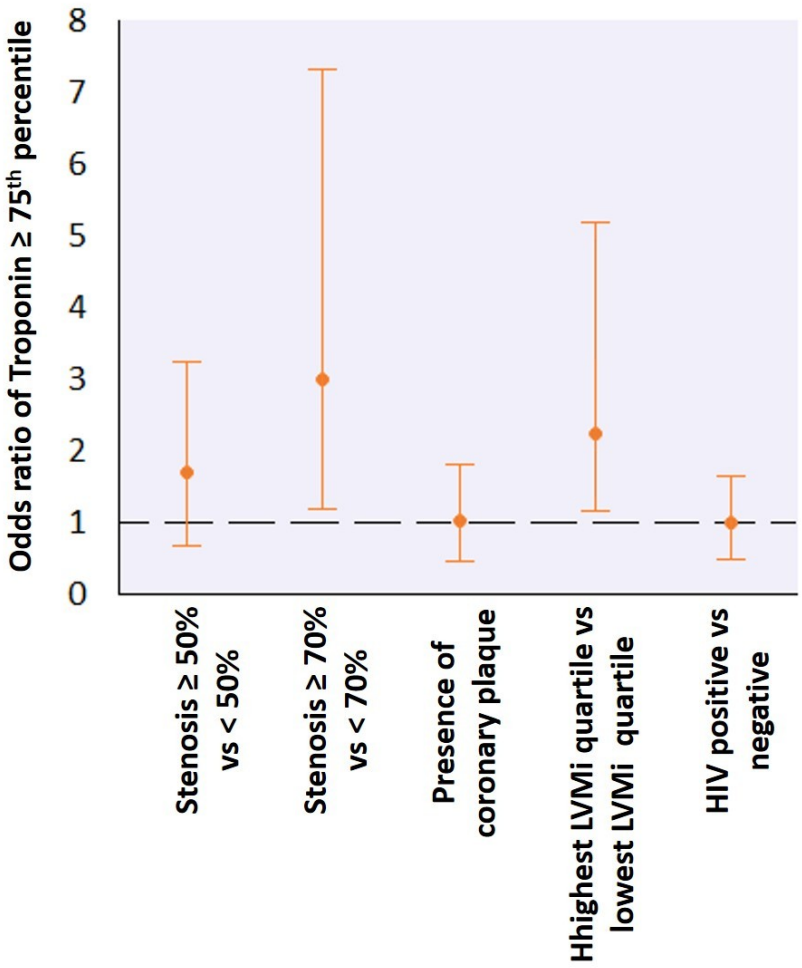

Figure 1. Odds ratios and 95% confidence intervals for elevated troponin levels (high-sensitivity troponin I ≥ 75th percentile) according to degree of coronary artery stenosis, presence of coronary plaque, indexed left ventricular mass quartiles, and HIV status. Multivariable-adjustment for age, race, education, center, body mass index, smoking status, pack years smoked, alcohol intake, systolic blood pressure, anti-hypertensive medication use, diabetes medication use, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and use of lipid lowering medications. LVMi = indexed left ventricular mass

Table 1. Characteristics of participants by troponin levels at the visit closest to CT scan

Characteristic	Overall	High-sensitivity troponin I (ng/L)				p-value
		1st Quartile (0.2-1.7)	2nd Quartile (1.8-2.3)	3rd Quartile (2.4-3.6)	4th Quartile (3.7-51.9)	
n	458	124	117	106	111	
Age (year)	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 y 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)	
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 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*						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 drinks/wk	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)	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	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 medications (%)	36 (7.9)	10 (8.1)	3 (2.6)	9 (8.7)	14 (12.6)	0.05
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‡	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 experienced (%)						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)	
Stenosis ≥ 50%	73 (16.3)	13 (10.5)	23 (20.0)	11 (10.8)	26 (24.1)	0.01
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
Non-calcified 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
Left ventricular hypertrophy† (%)	9 (2.0)	1 (0.8)	0 (0)	5(5.0)	3(2.8)	0.05

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

* 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).
† Left ventricular hypertrophy defined as ≥ 96g/m^2
‡ Detectable considered ≥ 50 copies/ml, proportion is of HIV infected participants
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor

Table 2. The association of high-sensitivity troponin I levels with coronary artery stenosis and indexed left ventricular mass

	N	Model 1	Model 2	Model 3	Model 4	Model 5
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)	0.08 (-0.09, 0.26)	0.08 (-0.10, 0.26)	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)	0.18 (-0.07, 0.42)	0.18 (-0.06, 0.43)	0.15 (-0.10, 0.40)
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)	-0.002 (-0.16, 0.16)	-0.01 (-0.17, 0.15)	-0.04 (-0.20, 0.12)
Stenosis ≥ 50%	73	0.11 (-0.06, 0.29)	0.10 (-0.07, 0.27)	0.08 (-0.10, 0.27)	0.08 (-0.10, 0.26)	0.05 (-0.13, 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)	-0.03 (-0.19, 0.12)	-0.04 (-0.20, 0.11)	
Presence of non-calcified plaque						
No	186	Ref	Ref	Ref	Ref	
Yes	272	0.02 (-0.10, 0.15)	-0.003 (-0.13, 0.12)	-0.02 (-0.14, 0.11)	-0.02 (-0.15, 0.11)	
Presence of mixed plaque						
No	293	Ref	Ref	Ref	Ref	
Yes	165	0.03 (-0.11, 0.16)	0.02 (-0.11, 0.15)	0.03 (-0.10, 0.17)	0.03 (-0.10, 0.17)	
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 (-0.08, 0.19)	0.06 (-0.08, 0.19)	
Structural heart disease						
Indexed LV mass < 96 g/m^2	432	Ref	Ref	Ref	Ref	Ref
Indexed LV mass ≥ 96 g/m^2	9	0.39 (-0.05, 0.83)	0.39 (-0.05, 0.82)	0.29 (-0.15, 0.73)	0.28 (-0.16, 0.72)	0.33 (-0.13, 0.80)
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 (0.01, 0.01)
Indexed LV mass*						
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)	0.05 (-0.13, 0.23)	0.05 (-0.13, 0.23)	0.04 (-0.14, 0.23)
Quartile 3 (54.4, 63.6)	112	0.28 (0.10, 0.45)	0.26 (0.08, 0.44)	0.21 (0.03, 0.40)	0.21 (0.03, 0.40)	0.21 (0.03, 0.40)
Quartile 4 (63.6, 120.4)	111	0.40 (0.22, 0.58)	0.37 (0.20, 0.55)	0.29 (0.11, 0.48)	0.29 (0.10, 0.48)	0.30 (0.11, 0.49)

Assessed using multivariable linear regression
Model 1: Adjusted for age, race, education, and center.
Model 2: Further adjusted for body mass index, smoking status, smoking pack/year, and alcohol intake.
Model 3: Further adjusted for systolic blood pressure, anti-hypertensive medication use, diabetes medication use, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and use of lipid lowering medications.
Model 4: Further adjusted for human immunodeficiency virus infection status.

Model 5: Stenosis further adjusted for left ventricular hypertrophy (indexed LV mass ≥ 96 g/m^2), and structural heart models further adjusted for stenosis (<70% or ≥70%).
* quartile parameters indicated in parenthesis in g/m^2
LV = left ventricular

Table 3. The association of high-sensitivity troponin I levels with coronary artery stenosis and indexed left ventricular mass by HIV serostatus

	HIV-infected				HIV-uninfected		
	N	**Model 1**	**Model 2**	**Model 3**	**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)	0.10 (-0.11, 0.32)	31	0.10 (-0.19, 0.40)	0.01 (-0.29, 0.32)	0.05 (-0.29, 0.38)
Stenosis categories 2								
Stenosis < 70%	252	Ref	Ref	Ref	162	Ref	Ref	Ref
Stenosis ≥ 70%	18	0.27 (-0.03, 0.57)	0.29 (-0.01, 0.58)	0.33 (0.02, 0.65)	16	0.11 (-0.27, 0.49)	0.02 (-0.36, 0.40)	0.07 (-0.35, 0.49)
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)	0.07 (-0.11, 0.25)	27	0.01 (-0.30, 0.32)	-0.07 (-0.39, 0.24)	-0.03 (-0.36, 0.30)
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)	0.04 (-0.30, 0.39)
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)	-0.01 (-0.19, 0.17)	129	0.07 (-0.18, 0.33)	-0.01 (-0.27, 0.26)	0.01 (-0.27, 0.29)
Presence of non-calcified 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)	0.09 (-0.14, 0.33)
Presence of mixed plaque								

No	179	Ref	Ref	Ref	114	Ref	Ref	Ref
Yes	99	-0.02 (-0.18, 0.13)	-0.002 (-0.16, 0.15)	0.03 (-0.13, 0.18)	66	0.15 (-0.09, 0.39)	0.12 (-0.12, 0.36)	0.12 (-0.15, 0.38)
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)	0.02 (-0.15, 0.18)	75	0.14 (-0.11, 0.39)	0.09 (-0.16, 0.34)	0.12 (-0.15, 0.39)
Structural heart disease								
LV 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 (-0.004, 0.84)	0.31 (-0.11, 0.74)	1	-0.30 (-1.78, 1.18)	-0.38 (-1.87, 1.10)	-0.42 (-1.93, 1.09)
Continuous indexed LV mass	441	0.01 (0.00, 0.01)	0.01 (0.00, 0.01)	0.01 (0.00, 0.01)		0.02 (0.01, 0.03)	0.02 (0.01, 0.02)	0.02 (0.01, 0.03)
Indexed LV mass*								
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)	0.01 (-0.21, 0.22)	39	0.19 (-0.13, 0.50)	0.16 (-0.16, 0.48)	0.22 (-0.13, 0.56)
Quartile 3 [54.4, 63.6]	62	0.24 (0.02, 0.47)	0.23 (0.01, 0.46)	0.17 (-0.06, 0.40)	50	0.33 (0.03, 0.63)	0.29 (-0.01, 0.59)	0.33 (0.01, 0.65)
Quartile 4 [63.6, 120.4]	69	0.30 (0.09, 0.52)	0.27 (0.06, 0.48)	0.20 (-0.03, 0.42)	42	0.56 (0.24, 0.87)	0.47 (0.15, 0.80)	0.47 (0.10, 0.83)

Model 1: Adjusted for age, race, education, and center.
Model 2: Further adjusted for body mass index, smoking status, smoking pack/year, and alcohol intake.
Model 3: Further adjusted for systolic blood pressure, anti-hypertensive medication use, diabetes medication use, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and use of lipid lowering medications.
* quartile parameters indicated in parenthesis in g/m^2
LV = left ventricular

Table 4. The association of high-sensitivity troponin I levels with HIV treatment variables

	N	Model 1	Model 2	Model 3
HIV-infected vs. HIV-uninfected	458	-0.02 (-0.15, 0.11)	0.02 (-0.11, 0.15)	0.06 (-0.07, 0.20)
HAART vs. No HAART in HIV-infected men	278	0.12 (-0.05, 1.30)	0.10 (-0.07, 0.28)	0.07 (-0.11, 0.25)*

HAART in HIV-infected men				
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)
Non-protease 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)	0.02 (-0.05, 0.08)*

Model 1: Adjusted for age, race, education, and center.
Model 2: Further adjusted for body mass index, smoking status, smoking pack/year, and alcohol intake.
Model 3: Further adjusted for systolic blood press, anti-hypertensive medication use, diabetes medication use, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and use of lipid lowering medications. *Further adjusted for $CD4^+$ (on HAART).
HAART = high active antiretroviral therapy;