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Subclinical myocyte injury, fibrosis and strain in relationship to coronary plaque in asymptomatic HIV-infected individuals

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Abstract

Background—Cardiovascular disease (CVD) rates are increased in HIV. The degree to which myocyte injury, strain and fibrosis occur prior to clinical disease and relate to coronary plaque in HIV is unknown.

Objective—To investigate newer cardiac biomarkers of subclinical myocyte injury (hs-cTnT), strain (NT-proBNP), fibrosis (sST2, Galectin-3) and vascular inflammation (oxLDL, Lp-PLA2) in HIV-infected individuals and non-HIV controls and relate these to coronary plaque by cardiac CT angiography (CCTA).

Design—Observational

Methods—Markers were investigated in 155 HIV-infected and 70 non-HIV-infected participants without known CVD and with low traditional CVD risk and related to CCTA data.

Results—Age, sex, race did not differ between the groups. hs-cTnT [3.1 (3.0, 6.4) vs. 3.0 (3.0, 4.0), P=0.03], Galectin-3 [13.5 (10.6, 18.1) vs. 11.6 (9.9, 14.5) P=0.002] and sST2 [31.5 (24.5,

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41.5) vs. 28.3 (20.2, 33.5) $P=0.01$] were significantly higher in HIV-infected participants vs. controls. Detectable hs-cTnT (seen in 50% of HIV participants) related to the overall presence of plaque (OR 2.3, $P=0.01$) and particularly to coronary calcium (OR for Agatston calcium score >0 , 3.3, $P=0.0008$ and OR for calcified plaque 7.4, $P=0.01$) in HIV, but not in non-HIV.

Conclusion—Subclinical myocyte injury is observed among young, asymptomatic HIV-infected individuals with low traditional cardiac risk factors. In the setting of HIV infection, the presence of detectable cardiac troponin is strongly associated with coronary plaque, particularly calcified plaque among an asymptomatic group. Future studies are needed to assess if early subclinical injury marked by hs-cTnT predicts plaque progression and cardiac events in HIV.

Keywords

cardiovascular diseases; HIV; biomarkers; atherosclerotic plaque

Introduction

Despite advances in medical care for people living with HIV, which include advances in treatment, decreased rates of AIDS-related deaths (1), and increased life expectancy (2,3), elevated rates of non-AIDS complications such as cardiovascular disease (CVD) are increasingly prevalent in this population (4,5). Large epidemiological studies have shown that rates of acute myocardial infarction (AMI) are 1.5 to 2 times higher in HIV patients compared to those without HIV even after controlling for traditional cardiovascular risk factors such as hypertension, diabetes, and smoking (6,7). Studies have postulated that non-traditional risk factors, such as increased inflammation (8,9) and immune activation (10–13) may contribute to the increased risk of CVD among people living with HIV. However, to our knowledge no such studies to date have evaluated cardiac specific biomarkers of myocyte injury and their relationships with atherosclerotic plaque detected by contrast-enhanced cardiac computed tomography angiography (CCTA). In this study, we evaluate for the first time novel cardiac biomarkers of myocyte injury, strain and fibrosis and assess relationships to coronary plaque characteristics in a cohort of HIV and non-HIV infected men and women.

Methods

Study Participants

One hundred and fifty five HIV-infected and seventy non-HIV-infected men and women aged 18–60 were enrolled between September 2006 and December 2012. Except for HIV disease, inclusion and exclusion criteria were identical for both groups. Exclusion criteria included history of cardiac disease or symptoms suggestive of any current or prior cardiac disease including angina, arrhythmias, valvular disease, pericarditis, or congestive heart failure, renal disease with creatinine level >1.5 mg/dL or creatinine clearance <60 mL/min. HIV-infected participants were on a stable antiretroviral (ART) regimen in the preceding 3 months. The Institutional Review Boards at both the Massachusetts General Hospital and Massachusetts Institute of Technology approved the study; written informed consent was provided by all study participants. Data from this cohort has been published previously (12–

16) and we now report novel data on markers of cardiac myocyte injury, stress, fibrosis, and vascular inflammation in relation to data on atherosclerosis.

Clinical and Sociodemographic Assessments

At enrollment, detailed information was collected on medical history and traditional cardiovascular disease risk factors including family history, and history of smoking and recreational drug use. Among HIV participants, HIV-related disease characteristics collected included duration of HIV infection, detailed antiretroviral therapy (ART) history, history of opportunistic infections and self-reported nadir CD4 count.

Cardiac Biomarker, Metabolic, and Immunologic Assessments

The following six soluble protein biomarkers were selected for measurement: high sensitivity troponin T (hs-cTnT), for myocardial injury; amino terminal proB-type natriuretic peptide (NT-proBNP), for assessment of hemodynamic myocardial stress; soluble ST2 (sST2), for adverse cardiac remodeling and tissue fibrosis; Galectin-3, for fibrosis and inflammation; oxidized LDL (oxLDL), for vascular atherosclerosis; and lipoprotein-associated phospholipase A2 (Lp-PLA2), for vascular inflammation. Hs-cTnT and NT-proBNP were measured using specific reagents for the Cobas e 601 instrument system (both from Roche Diagnostics, Indianapolis, IN, USA). The measurement range for hs-cTnT was from 3.0 to 10,000 ng/L. Inter-assay coefficients of variation (CVs) ranged from 3.6% to 2.3% at values between 28 ng/L and 4962 ng/L. Hs-cTnT measurements with the Cobas e601 instrument are superior due to an additional wash step that improves the assay's signal-to-noise ratio. For the NT-proBNP assay, the measurement range was from 5.0 to 35,000 pg/mL; inter-assay CVs ranged from 3.7% to 4.1% at values between 135 pg/mL and 4130 pg/mL. ELISA measurements for the following biomarkers were performed in strict accordance with manufacturer instructions: sST2 (Critical Diagnostics, San Diego, CA, USA); Galectin-3 (BG-Medicine, Waltham, MA, USA) and oxLDL (Mercodia, Uppsala, Sweden). For ST2, the assay measurement range was 3.1 to 200.0 ng/mL; the inter-assay CVs ranged from 8.9% to 7.3% at values between 20 ng/mL and 79.0 ng/mL. The Galectin-3 assay's measurement range is 0.96 to 130 ng/mL; inter-assay CVs ranged from <10% to 15% at values between 6 ng/mL and 70 ng/mL (17). The oxLDL method used had a measurement range of 8 to 150 U/L. Inter-assay CVs ranged from 8.3% to 7.4% at values between 8.5 U/L and 32 U/L. Lp-PLA2 was quantified with activity assay reagents (Diadexus, South San Francisco, CA) on a Vista Dimension 1500 system (Siemens Healthcare Diagnostics, Glasgow, DE, USA). The Lp-PLA2 assay has a measurement range of 10 to 400 nmol/min/mL and inter-assay CVs were 1.7 to 3.2% at values between 97–304 nmol/min/mL.

Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and glucose were quantified using standard techniques. CD4+ T-cell counts were assessed with flow cytometry and HIV-1 RNA was determined with ultrasensitive reverse-transcriptase polymerase chain reaction (Roche COBAS Amplicor; lower limit of detection, 50 copies/mL). All laboratory assessments were obtained after a 12 hour fast.

Cardiac Computed Tomography Angiography

Cardiac computed tomography angiography (CCTA) imaging was performed using a 64-slice dual-source CT scanner (Siemens Medical Solutions, Malvern, PA, USA). The CCTA protocol has been described previously (13,14)(18). This protocol included a non-contrast CT for calculation of Agatston calcium score (19) and contrast-enhanced retrospectively-ECG gated CCTA for assessment of calcified and noncalcified coronary plaque segments. In addition, cine images were reconstructed throughout each phase of the cardiac cycle to assess ventricular function. An experienced cardiac radiologist reviewed the images to calculate the Agatston calcium score, for noncalcified or mixed coronary plaque, presence of moderate (50–69%) or severe (≥70%) stenosis, and for qualitative assessment of left ventricular function on a dedicated workstation (Siemens Syngo MMWP). Abnormal left ventricular systolic function was defined as an estimated left ventricular ejection fraction < 50%.

Statistical Analysis

Distribution of variables was assessed via histograms and application of the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard error of the mean (SEM) whereas non-normally distributed data are presented as median (interquartile range, IQR). All categorical variables are reported as proportions. Comparisons were made first between HIV-infected and non-HIV-infected participants using the Student t test for normally distributed continuous variables, the Wilcoxon rank sum test for non-normally distributed data, and the χ^2 test for categorical variables. A sensitivity analysis controlled for statin use in each group. Levels of each biomarker were determined for those with and without plaque, and by presence of noncalcified plaque, presence of mixed plaque, and presence of calcified plaque, stratified by HIV status, using the Wilcoxon rank sum test. Correlations between the markers were determined using Spearman rank correlation coefficients, stratified by HIV status. To further assess the relationship of detectable hs-cTnT to plaque, we determined the odds ratio (OR) and corresponding 95% confidence intervals (CI) for the presence of overall plaque, noncalcified, mixed and calcified plaque as well as for various strata of Agatston calcium score for detectable vs. undetectable hs-cTnT, again stratifying our results by HIV status. Supplemental sensitivity analyses were performed controlling for gender and statin use. A supplemental analysis of biomarkers concentrations among HIV-infected and uninfected participants stratified by sex was also performed. All statistical analyses were performed using SAS JMP software (version 11.0; SAS Institute, Cary, NC, USA).

Results

Demographic and Clinical Characteristics of HIV-Infected and Non-HIV-Infected Participants

Results of demographic and clinical assessments are described in Table 1. Age, race, sex and traditional cardiovascular disease risk factors, including family history of premature coronary heart disease, hypertension, diabetes mellitus, current smoking, and active intravenous drug and cocaine use did not differ significantly between HIV-infected and non-HIV-infected participants. Ten-year Framingham risk was low in each group: 3% and 4%, non-HIV and HIV respectively. Current statin use was low in each group but slightly higher

among the HIV-infected participants (14% vs. 4%, $P=0.04$). HIV-infected participants demonstrated a mean duration of HIV infection of 14 years and mean CD4⁺ cell count 552 cells/ μ L. 86% of participants had an undetectable HIV-1 RNA viral load. Current use of PI, NRTI, and NNRTI treatments was 55%, 95%, and 37%, respectively. With respect to metabolic parameters, HIV-infected participants demonstrated increased triglycerides compared to the non-infected participants. BMI was not different between the two groups.

Coronary Artery Calcium Score and Coronary Plaque Characteristics among HIV-Infected and Non-HIV-Infected Participants

Consistent with our previously reported data, the prevalence of atherosclerotic plaque was significantly higher among HIV-infected participants compared to non-HIV-infected participants (54 vs. 38%, $P = 0.04$); similarly, the prevalence of noncalcified plaque (44 vs. 23%, $P = 0.004$) was also significantly higher among those with HIV. Calcified plaque and Agatston calcium score were similar between the groups (Supplemental Table 1) (13,14). Systolic function was assessed to be normal in 100% of non-HIV participants and 98% of HIV patients, and was not significantly different between the groups.

Cardiac Biomarkers of Myocyte Injury, Strain and Fibrosis among HIV-Infected and Non-HIV-Infected Participants

Hs-cTnT [3.1 (3.0, 6.4) vs. 3.0 (3.0, 4.0) ng/L, $P=0.03$], Galectin-3 [13.5 (10.6, 18.1) vs. 11.6 (9.9, 14.5) ng/mL, $P=0.002$] and sST2 [31.5 (24.5, 41.5) vs. 28.3 (20.2, 33.5) ng/mL, $P=0.01$] were significantly higher in HIV vs. non-HIV participants (Table 2, Figure 1), while NT-proBNP, LpPLA2, and oxLDL were not different between the two groups (Table 2). The differences persisted when controlling for statin use. The percent of participants with an hs-cTnT of >3 ng/L was not different between HIV vs. non-HIV, 50 vs. 41% ($P=0.22$).

In sex stratified analyses, differences in hs-cTnT, sST2, and Galectin-3 were more pronounced in the comparisons between HIV-infected vs. non-HIV-infected men. Hs-cTnT was most elevated among HIV-infected men across all groups. Systematic differences between these markers were not observed comparing HIV-infected vs. non-HIV-infected women (Supplemental Table 2).

Cardiac Biomarkers and Coronary Plaque Characteristics among HIV-Infected and Non-HIV-Infected Participants

HIV-Infected Participants—HIV-infected participants with any coronary plaque vs. those with no plaque detected by CCTA had significantly higher hs-cTnT [3.9 (3.0, 8.7) vs. 3.0 (3.0, 5.1) ng/L, $P=0.01$, with plaque vs. without plaque,], oxLDL [46.4 (37.4, 54.9) vs. 42.1 (31.9, 51.4) U/L, $P=0.04$] and Lp-PLA2 [199.1(159.4, 252.8) vs. 173.9 (143.1, 206.3) nmol/min/ml, $P=0.01$]. In further, assessment of plaque phenotype, those with mixed plaque demonstrated higher hs-cTnT [3.9 (3.0, 10.6) vs. 3.0 (3.0, 5.9) ng/L, $P=0.009$, with mixed plaque vs. without mixed plaque]. Similarly, those with calcified plaque also had higher hs-cTnT, [5.2 (3.5, 12.6) vs. 3.0 (3.0, 6.0) ng/L, $P=0.005$, with calcified plaque vs. without calcified plaque] (Table 3). Lower levels of Galectin-3 were observed among the HIV-infected participants with noncalcified plaque [11.8 (10.1, 14.9) vs. 14.0 (10.7, 17.6),

ng/mL, $P=0.04$] (Table 3). Only 2 HIV participants had evidence of abnormal systolic function and hs-cTnT was detectable in these patients.

Non-HIV-Infected Participants—No differences in hs-cTnT, NT-proBNP or fibrosis markers were seen among the non-HIV-infected participants, when stratifying by presence of plaque or type of plaque. However, higher levels of oxLDL were observed among non-HIV participants with vs. without noncalcified plaque [53.6 (49.5, 65.6) vs. 42.4 (34.3, 55.4) U/L, $P=0.008$] and mixed plaque [55.7 (40.9, 66.6) vs. 42.7 (34.4, 54.2) U/L, $P=0.01$]. Lp-PLA2 was also higher among those with noncalcified plaque [215.5 (170.1, 228.5) vs. 172.7 (146.2, 200.0), nmol/min/ml, $P=0.01$] (Table 3).

Relationship between Detectable hs-cTnT and Presence of Plaque in HIV-Infected and Non-HIV-Infected Participants

Detectable hs-cTnT but not markers of fibrosis or strain, related strongly to the overall presence of plaque [OR 2.3 (1.2, 4.6), $P=0.01$] and particularly to calcified plaque (OR for Agatston calcium score > 0 , 3.3 (1.7, 6.8), $P=0.0008$ and OR for presence of calcified plaque 7.4 (1.9, 48.3), $P=0.01$) in the HIV-infected group, but not among non-HIV controls. Stated differently, HIV patients with detectable vs. non-detectable hs-cTnT were approximately 50% more likely to have plaque based on prevalence rate ratios (Table 4). The OR for detectable hs-cTnT increased with increasing Agatston calcium score thresholds (Table 4). Associations between hs-cTnT and plaque remained largely significant in sensitivity analyses controlling for gender and statin use (Supplemental Table 3).

Correlations between Cardiac Biomarkers among HIV-infected and Non-HIV-Infected Participants

Among the HIV participants, hs-cTnT associated with sST2, whereas NT-ProBNP related to sST2 and Galectin-3 (all $P<0.05$); as expected, oxLDL and LpPLA2 were also correlated (Supplemental Table 4). With respect to correlations of biomarkers with HIV-specific parameters, Galectin-3 related to CD4 (-0.17, $P=0.04$), while none of these markers related to viral load (data not shown). Among non-HIV participants, oxLDL was found to correlate with LpPLA2 and NT-ProBNP (Supplemental Table 4).

Discussion

In this study, we examined novel biomarkers of myocyte injury, strain, generalized fibrosis and vascular inflammation and their relationships to coronary plaque characteristics in a cohort of HIV and non-HIV infected men and women without any history of CVD and with low traditional cardiovascular risk scores. We show for the first time that hs-cTnT, sST2, and Galectin-3 are significantly elevated among asymptomatic HIV patients in this group. These biomarkers were non-normally distributed in each group and the data in this study show a much more consistent clustering of these markers at the lower end of the assay ranges in the non HIV group, with a greater skewing of the distribution toward increased values among the HIV group. We also demonstrate that the HIV participants with plaque had higher levels of hs-cTnT compared to those without plaque. Examining plaque phenotypes within the HIV and non-HIV groups, HIV participants with mixed plaque and calcified plaque had

significantly elevated hs-cTnT levels, whereas these relationships were not seen among the non-HIV patients. Comparing the prevalence of plaque among those with and without detectable troponin, we show a significantly increased likelihood of having plaque based on detectable troponin, suggesting an association between hs-cTnT and subclinical atherosclerosis among HIV patients. It is noteworthy that the assay system used for hs-cTnT measurement in this study is technically superior to earlier versions of the assay, and provided hs-cTnT measurements that were ~2-fold more sensitive and precise. Such a technical advantage likely translated into more accurate classification of participants in this study.

In the analysis stratified by sex, our findings demonstrated that there were no differences in markers observed between HIV-infected and non-HIV infected women other than for LpPLA2. In contrast differences in hs-cTnT, Galectin-3, and sST2 were evident comparing HIV-infected and non-HIV-infected men as were differences between women and men regardless of HIV status for many markers. Our findings confirm what is known in the general population, that there are sex differences between these cardiac biomarkers (20), however, no study to our knowledge has assessed these markers in HIV stratifying by sex. Studies to date conducted among HIV participants have included women exclusively in their analysis (21) or include women but do not stratify by sex. More research is needed to developing sex specific biomarker cutoffs for distinguishing heightened cardiovascular risk among HIV-infected women and men.

The findings that hs-cTnT levels were 3 ng/L (within the detectable range in a high sensitivity assay) in at least half of relatively young, HIV infected adults with well controlled HIV infection and without CVD, that levels are higher compared to demographic and risk factor-matched non-infected controls, and that hs-cTnT is most strongly associated with calcified versus noncalcified plaque in the HIV group are consistent with several lines of evidence from general and diabetic population studies. However, in the current study, relationships of plaque to hs-cTnT were even stronger among HIV-infected compared to non-HIV participants.

In a predominantly middle aged adult population participating in the Dallas Heart Study, careful phenotyping with cardiac magnetic resonance imaging (CMR) for left ventricular structure and cardiac CT for coronary calcium showed in univariate analyses that hs-cTnT was associated with both the extent of coronary calcium and progressively greater left ventricular mass (22). In the Dallas cohort, only 24.2% of individuals in the 40–49 age range had an hs-cTnT $\geq$ 3.0 ng/L, suggesting that HIV-infected patients have a much higher prevalence of detectable hs-cTnT than a similar age general population cohort.

What are the mechanisms of increased troponin, indicative of subclinical myocyte injury that we observed among HIV-infected patients in the current study? Increased hs-cTnT is unlikely to be due to atherothrombotic events in our relatively young, asymptomatic HIV population. The lack of association with noncalcified plaque further supports this observation. In the general population, there has been some controversy, but the weight of the evidence shows a stronger association between hs-cTnT and coronary calcium than noncalcified plaque (23–26). Among patients presenting with chest pain, but without an

acute coronary syndrome, Januzzi et al. observed that hs-cTnT was strongly associated with calcified plaque, but had only a borderline association with noncalcified plaque (26). In the study of Januzzi et al., left ventricular mass again remained an independent predictor of hs-cTnT in multivariate regression analysis while coronary calcium did not (26). In the current study, the vast majority of HIV patients had normal left ventricular systolic function, as assessed by CT, suggesting that the increases in hs-cTnT are therefore not due to any clinically significant decreases in systolic function, in this young population.

Recent findings in diabetics with coronary disease have also reinforced the observation that elevations of hs-cTnT in the setting of chronic disease is unlikely to be the result of atheroembolic events (27). In a substudy of the BARI-2D trial, higher hs-cTnT levels (in the absence of an acute coronary syndrome) were associated with a poorer prognosis; moreover, coronary revascularization neither decreased the hs-cTnT level nor modified the poor prognosis associated with their elevation (27). In the current study we measured a high sensitivity troponin for the first time in an HIV-infected cohort and observed no association between hs-cTnT and noncalcified plaque, but instead observed a strong association with coronary calcium. Moreover there was a progressive increase in the strength of the association between hs-cTnT and plaque, based on greater calcium content.

In contrast to hs-cTnT, oxLDL level was significantly associated with noncalcified plaque in non-HIV subjects and trended toward a significant association with noncalcified plaque in the HIV infected group. Interestingly, differences in oxLDL levels based on the presence or absence of plaque diminished in the HIV-infected subjects with progressive increases coronary calcium, moving in the opposite direction of the observed findings with hs-cTnT.

There is an established link between non-atherosclerotic coronary calcium and subclinical myocardial pathology that may serve to explain the association between hs-cTnT and coronary calcium in our cohort. In the Multi-Ethnic Study of Atherosclerosis (MESA) general population study of participants without clinical cardiovascular disease, a high ankle brachial index measure indicative of arterial stiffness and medial arterial calcification was associated with higher CAC scores and greater LV mass (28). Left ventricular mass is typically greater in HIV patients compared to age and sex-matched controls (29) and may be a link to coronary calcium through a process of medial arterial calcification of the vasculature in the HIV population.

In an era of well controlled HIV disease, systolic heart failure has largely disappeared, but has been replaced by a high prevalence of mild to moderate diastolic dysfunction at an age much younger than would be expected to be found in the general population (29,30). Along with hs-cTnT, we observed that ST2 was increased in HIV versus non-HIV-infected controls. Unlike hs-cTnT, however, ST2 was not associated with coronary calcium or plaque. In the general population, ST2 was not associated with increased left ventricular mass among patients referred for echocardiography (31). Recently, in an HIV positive cohort, ST2 was found to be strongly associated with diastolic dysfunction and mortality (32). In animal studies, soluble ST2 measured in the circulation is thought to act as a decoy receptor for the ST2 ligand which binds interleukin-33 (IL-33) (33). The membrane bound ST2-IL33 interaction has an anti-fibrotic effect in the myocardium and higher levels of circulating

soluble ST2 are associated with increased myocardial fibrosis (34). Galectin-3 levels were also higher in HIV infected participants. The mechanism is likely complex in that *in-vitro* data suggests HIV-infected T-cells increase Galectin-3 expression by the viral regulatory gene *tat* (35). Galectin-3 has been shown to induce myocardial fibrosis in animal models and is highly upregulated in heart failure (36). Higher Galectin-3 levels have also been associated with increased left ventricular mass in the Framingham Heart Study (37). Increased subclinical myocardial pathology in HIV-infected patients, in the form of inflammation and interstitial fibrosis, was observed in two cardiac magnetic resonance studies (38,39). This pathology is likely independent of coronary atherosclerotic disease and may be reflected in elevated levels of hs-cTnT, Galectin-3 and ST2.

Despite elevated levels of the cardiac specific injury marker hs-cTnT and two soluble non-cardiac specific markers that could reflect increased fibrosis, NT-proBNP levels, a cardiac specific marker of strain, was not different between HIV infected and non-infected patients. This may simply be a reflection of the early stage of the myocardial disease process as natriuretic peptide levels are thought to be best reflected by end-diastolic wall stress that may still be within normal limits for both groups(40).

Accelerated atherosclerotic coronary disease has been frequently documented in patients with well controlled HIV infection and has resulted in the large multi-center NIH funded primary prevention of cardiovascular events, the REPRIEVE trial. In this era of well controlled HIV infection, the extent to which there is concomitant progressive myocardial disease that is independent of coronary atherosclerosis is in large part unknown. We demonstrate an increase in subclinical myocyte injury in HIV. Of particular concern is the finding that observed levels hs-cTnT, an established risk marker, are equivalent to levels observed in subjects a decade older in the general population (41). Further work will need to be done to replicate these findings, better understand the natural history associated with this biomarker through longitudinal follow-up and investigate the interplay with atherosclerotic events. Ultimately, it needs to be determined if these biomarkers can be used as an early signal to predict adverse cardiac events, including heart failure or death, and serve as a trigger for initiating therapy to prevent progression to these outcomes.

Strengths of our study include the assessment of cardiac specific biomarkers of myocyte injury, strain and fibrosis and their relationships to coronary plaque characteristics assessed by CCTA. Moreover, the inclusion of well-matched controls of both genders allows for valuable comparisons in biomarkers of myocyte injury in the non-HIV population. We show for the first time that hs-cTnT, an index of myocyte injury, is elevated in HIV-infected participants, even those without known CVD and with low CVD risk and grossly normal systolic function. Our data demonstrate that hs-cTnT levels relate strongly to presence of calcified plaque, suggesting potential utility of hs-cTnT as an indicator of coronary plaque in this population. Limitations of our study include the observational design, which allows for investigation of associations but does not allow for determination of causality or ability of these biomarkers to predict CVD. Moreover, the stronger associations between these markers and plaque might be due to the higher prevalence of plaque in HIV or other as yet unknown factors unique to HIV. The strong associations were not the result so any differences in statin use, but gender specific affects were seen. Future longitudinal studies

are now needed to assess the clinical relevance of increased subclinical myocyte injury markers in the HIV population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Distribution of hs-cTnT, Galectin-3, and ST2 among HIV-infected and non-HIV infected participants. Dots represent individual participants, the gray shading represents the density of the distribution of the dots for participants. The density of the distribution allows for visual comparisons between groups. For demonstration purposes, hs-cTnT axis was abbreviated to 50 ng/L however, 1 outlier exceeded this level. See Table 2 for mean $\pm$ SEM values. hs-cTnT, high-sensitivity cardiac troponin T; sST2, soluble ST2

Table 1

Characteristics of Non-HIV-Infected and HIV-Infected Participants

	Non-HIV-Infected Participants (n=70)	HIV-Infected Participants (n=155)	P-value
Demographics			
Age, y	46 ± 1	47 ± 1	0.17
Sex			
Male	59%	61%	0.70
Race			
Non-Caucasian	51%	51%	0.95
Framingham Total Point Score	8 ± 1	9 ± 0	0.12
Family history of premature CHD by NCEP	24%	21%	0.65
Hypertension	16%	24%	0.18
Current statin treatment	4%	14%	0.04
Diabetes mellitus	7%	10%	0.44
Current smoker	40%	44%	0.56
Menopausal	44%	47%	0.79
Active IVDU	3%	3%	0.91
Active Cocaine Use	6%	9%	0.40
HIV Disease Related Parameters			
Duration since HIV diagnosis, y		14 ± 1	N/A
Currently on antiretroviral therapy		99%	N/A
Duration of antiretroviral therapy, y		8 ± 0	N/A
Current PI treatment		55%	N/A
Duration of PI treatment, y		4 ± 0	N/A
Current NRTI treatment		95%	N/A
Duration of NRTI treatment, y		7 ± 0	N/A
Current NNRTI treatment		37%	N/A
Duration of NNRTI treatment, y		3 ± 0	N/A
CD4+ T-lymphocytes, cells/μL		552 ± 24	N/A
Nadir CD4+ T-lymphocytes, cells/μL		193 ± 15	N/A
Log HIV RNA viral load, copies/mL		1.8 ± 0.04	N/A
Undetectable HIV RNA < 50 copies/mL		86%	N/A
Anthropometric and Metabolic Indices			
Body mass index, kg/m ²	28 ± 1	27 ± 0	0.31
Creatinine, mg/dL	0.95 ± 0.03	0.97 ± 0.02	0.52
Systolic blood pressure, mm Hg	117 ± 2	119 ± 1	0.16
Diastolic blood pressure, mm Hg	76 ± 1	76 ± 1	0.62
Fasting glucose, mg/dL	88 ± 1	92 ± 2	0.14
Hemoglobin A1c, %	5.6 ± 0.1	5.5 ± 0.1	0.15
Total cholesterol, mg/dL	180 ± 4	183 ± 4	0.53
HDL cholesterol, mg/dL	53 ± 2	53 ± 1	0.93
LDL cholesterol, mg/dL	106 ± 4	102 ± 3	0.39

	Non-HIV-Infected Participants (n=70)	HIV-Infected Participants (n=155)	P-value
Triglycerides, mg/dL	102 ± 7	138 ± 9	0.002

Data reported as mean ± standard error of the mean, percentage or median (interquartile range). Abbreviations: CHD, coronary heart disease; NCEP, National Cholesterol Education Program; IVDU, intravenous drug use; PI, protease inhibitor; N/A, not applicable; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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Table 2
Cardiac Biomarkers of Myocyte Injury, Strain, Fibrosis and Vascular Inflammation

	Non-HIV-Infected (n=70)	HIV-Infected (n=155)	P-value	P-value for HIV Status (controlling for Statin Use)
Log of hs-cTnT	0.56 ± 0.02	0.68 ± 0.02	0.0004	0.005
hs-cTnT, ng/L	3.0 (3.0, 4.0)	3.1 (3.0, 6.4)	0.03	0.10
NT-proBNP, pg/mL	23.8 (12.9, 52.7)	27.9 (14.5, 61.8)	0.37	0.82
Galectin-3, ng/mL	11.6 (9.9, 14.5)	13.5 (10.6, 18.1)	0.002	0.001
sST2, ng/mL	28.3 (21.1, 33.5)	31.5 (24.5, 41.5)	0.01	0.01
Oxidized LDL, U/L	44.4 (35.8, 56.4)	43.9 (33.4, 53.5)	0.48	0.49
Lp-PLA2 activity, nmol/min/ml	172.9 (146.7, 216.6)	184.3 (152.6, 229.7)	0.12	0.11

Data reported as mean ± standard error of the mean or median (interquartile range)

hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, amino terminal proB-type natriuretic peptide;

sST2, soluble ST2; Lp-PLA2, lipoprotein-associated phospholipase A2

Table 3

Markers and Coronary Plaque Characteristics

Parameter	Presence of Plaque		P-value	Presence of Noncalcified Plaque		P-value	Presence of Mixed Plaque		P-value	Presence of Calcified Plaque		P-value
	No	Yes		No	Yes		No	Yes		No	Yes	
LDL	3.0 (3.0, 3.8)	3.2 (3.0, 5.0)	0.32	3.0 (3.0, 3.8)	3.5 (3.0, 5.1)	0.17	3.0 (3.0, 3.8)	3.2 (3.0, 5.1)	0.28	3.0 (3.0, 3.8)	3.3 (3.0, 5.1)	0.23
LDL	23.1 (10.8, 59.5)	22.4 (13.4, 37.2)	0.70	24.0 (12.3, 55.6)	22.3 (13.3, 33.1)	0.53	22.3 (11.3, 54.9)	23.5 (13.4, 40.0)	0.97	22.3 (12.7, 51.9)	32.5 (13.0, 77.8)	0.75
LDL	11.9 (9.9, 0)	11.1 (9.6, 15.2)	0.75	11.8 (9.9, 14.5)	11.2 (9.0, 13.3)	0.77	11.6 (9.8, 13.4)	11.9 (9.8, 17.2)	0.30	11.9 (9.9, 14.4)	10.6 (9.1, 14.2)	0.49
LDL	28.5 (20.1, 33.0)	26.9 (19.0, 36.4)	0.91	28.3 (19.9, 33.1)	26.9 (19.2, 36.4)	0.83	28.0 (20.2, 33.0)	28.4 (18.0, 36.8)	0.80	28.0 (19.7, 33.4)	31.4 (22.2, 36.4)	0.56
LDL	43.8 (34.3, 7)	51.4 (38.8, 64.8)	0.05	42.4 (34.3, 55.4)	53.6 (49.5, 65.6)	0.008	42.7 (34.4, 54.2)	55.7 (40.9, 66.6)	0.01	44.6 (37.5, 56.2)	49.7 (35.2, 65.2)	0.51
min/ml	172.8 (141.1, 207.9)	187.4 (161.1, 223.2)	0.11	172.7 (146.2, 200.0)	215.5 (170.1, 228.5)	0.01	175.2 (144.3, 215.1)	188.8 (160.1, 225.7)	0.14	172.8 (146.9, 215.1)	186.3 (171.0, 221.0)	0.31

Parameter	Presence of Plaque		P-value	Presence of Noncalcified Plaque		P-value	Presence of Mixed Plaque		P-value	Presence of Calcified Plaque		P-value
	No	Yes		No	Yes		No	Yes		No	Yes	
LDL	3.0 (3.0, 5.9)	3.9 (3.0, 8.7)	0.01	3.0 (3.0, 6.0)	3.7 (3.0, 8.3)	0.18	3.0 (3.0, 5.9)	3.9 (3.0, 10.6)	0.009	3.0 (3.0, 6.0)	5.2 (3.5, 12.6)	0.005
LDL	25.6 (14.5, 43.5)	27.3 (12.4, 63.0)	0.92	26.5 (14.5, 46.7)	25.2 (12.1, 64.3)	0.73	25.3 (13.8, 41.6)	32.1 (12.6, 72.0)	0.28	25.5 (12.8, 54.1)	33.5 (19.2, 95.4)	0.18
LDL	13.8 (10.6, 15.8)	12.8 (10.1, 17.2)	0.36	14.0 (10.7, 17.6)	11.8 (10.1, 14.9)	0.04	13.4 (10.2, 16.6)	12.8 (10.2, 18.3)	0.89	13.4 (10.2, 17.2)	11.5 (10.1, 17.3)	0.67
LDL	32.1 (25.1, 42.4)	31.0 (24.6, 40.4)	0.63	31.2 (25.3, 42.0)	31.5 (24.2, 40.3)	0.65	31.8 (24.4, 41.2)	30.8 (25.2, 41.1)	0.88	31.8 (24.5, 41.0)	30.1 (26.5, 41.6)	0.80
LDL	42.1 (31.9, 51.4)	46.4 (37.4, 54.9)	0.04	43.4 (32.2, 51.6)	47.4 (37.1, 55.5)	0.09	43.7 (32.3, 51.8)	45.4 (37.4, 58.1)	0.08	44.8 (33.6, 53.7)	42.1 (36.5, 51.4)	0.93
min/ml	173.9 (143.1, 206.3)	199.1 (159.4, 252.8)	0.01	179.9 (146.4, 217.3)	196.0 (158.5, 251.0)	0.13	177.8 (144.8, 217.1)	217.0 (160.4, 250.1)	0.01	186.5 (153.2, 236.3)	209.4 (155.4, 229.5)	0.47

s median (interquartile range)

LDL: low-density lipoprotein; NT-proBNP: amino terminal proB-type natriuretic peptide; sST2: soluble ST2; Lp-PLA2: lipoprotein-associated phospholipase A2

Table 4
Relationships of hs-cTnT to Atherosclerosis Characteristics Among HIV-infected and Non-HIV-Infected Participants

	Agatston calcium score > 0	Agatston calcium score 100	Presence of Coronary Plaque	Presence of Noncalcified Plaque	Presence of Mixed Plaque	Presence of Calcified Plaque	Presence of Moderate Stenosis	Presence of Severe Stenosis
Non-HIV-Infected								
Detectable hs-cTnT[‡]	38%	17%	45%	31%	34%	24%	4%	N/A
Undetectable hs-cTnT	26%	5%	32%	17%	22%	13%	3%	N/A
OR (95% CI)	1.7 (0.6, 4.9)	3.8 (0.7, 27.7)	1.7 (0.6, 4.7)	2.3 (0.7, 7.7)	1.8 (0.6, 5.7)	2.1 (0.6, 7.9)	1.2 (0.0, 32.4)	N/A
P-value	0.31	0.13	0.30	0.18	0.28	0.25	0.88	N/A
HIV-Infected								
Detectable hs-cTnT[‡]	49%	12%	64%	49%	45%	18%	16%	7%
Undetectable hs-cTnT	23%	1%	43%	37%	23%	3%	6%	0%
OR (95% CI)	3.3 (1.7, 6.8)	10.1 (1.8, 188.5)	2.3 (1.2, 4.6)	1.6 (0.8, 3.2)	2.8 (1.4, 5.8)	7.4 (1.9, 48.3)	3.0 (1.0, 11.2)	N/A
P-value	0.0008	0.03	0.01	0.14	0.006	0.01	0.07	N/A

hs-cTnT, high-sensitivity cardiac troponin T

[‡] hs-cTnT <2.99 ng/L is undetectable

^{\$} Moderate stenosis equals >50% and 69% stenosis

^{*} Severe stenosis equals 70% stenosis