ORIGINAL RESEARCH

HIV Infection Itself May Not Be Associated With Subclinical Coronary Artery Disease Among African Americans Without Cardiovascular Symptoms

Hong Lai, PhD; Richard Moore, MD; David D. Celentano, ScD; Gary Gerstenblith, MD; Glenn Treisman, MD; Jeanne C. Keruly, MS; Thomas Kickler, MD; Ji Li, MD; Shaoguang Chen, MS; Shenghan Lai, MD; Elliot K. Fishman, MD

***Background*—**The key objectives of this study were to examine whether HIV infection itself is associated with subclinical coronary atherosclerosis and the potential contributions of cocaine use and antiretroviral therapies (ARTs) to subclinical coronary artery disease (CAD) in HIV-infected persons.

***Methods and Results*—**Between June 2004 and February 2015, 1429 African American (AA) adults with/without HIV infection in Baltimore, Maryland, were enrolled in an observational study of the effects of HIV infection, exposure to ART, and cocaine use on subclinical CAD. The prevalence of subclinical coronary atherosclerosis was 30.0% in HIV-uninfected and 33.7% in HIV-infected (P=0.17). Stratified analyses revealed that compared to HIV-uninfected, HIV-infected ART naïve were at significantly lower risk for subclinical coronary atherosclerosis, whereas HIV-infected long-term ART users (≥36 months) were at significantly higher risk. Thus, an overall nonsignificant association between subclinical coronary atherosclerosis and HIV was found. Furthermore, compared to those who were ART naïve, long-term ART users (≥36 months) were at significantly higher risk for subclinical coronary atherosclerosis in chronic cocaine users, but not in those who never used cocaine. Cocaine use was independently associated with subclinical coronary atherosclerosis.

***Conclusions*—**Overall, HIV infection, per se, was not associated with subclinical coronary atherosclerosis in this population. Cocaine use was prevalent in both HIV-infected and -uninfected individuals and itself was associated with subclinical disease. In addition, cocaine significantly elevated the risk for ART-associated subclinical coronary atherosclerosis. Treating cocaine addiction must be a high priority for managing HIV disease and preventing HIV/ART-associated subclinical and clinical CAD in individuals with HIV infection. **(*J Am Heart Assoc*. 2016;5:e002529 doi: 10.1161/JAHA.115.002529)**

Key Words: African American • antiretroviral therapy • cocaine use • coronary CT angiography • HIV infection • subclinical coronary atherosclerosis

Despite that in vivo and in vitro evidence demonstrates that HIV directly infects human arterial smooth muscle cells and may contribute to the pathogenesis of atherosclerosis in HIV-infected individuals,[1] the relationship between HIV infection and coronary artery disease (CAD) risk in HIV-infected patients remains controversial because of differences in patient characteristics and study design.[2–4] In addition, underdetection of clinical CAD is an inherent shortcoming when clinical disease is used as a study outcome given that one third of myocardial infarctions (MIs) in the Framingham Heart Study were unrecognized by participants and their physicians when they occurred.[5] Subclinical atherosclerosis has been investigated in relation to HIV infection, exposure to antiretroviral therapy (ART), chronic drug abuse, and other factors using noninvasive cardiac computed tomography (CT) imaging.[6–14] The findings from these studies are not consistent. For example, the prevalence of coronary artery stenoses in excess of 70% in HIV-infected men was reported[14] whereas other studies reported much lower rates.[10,12] It has been speculated that HIV infection per se may not affect the pathogenetic process leading to CAD, but instead, be a "marker" to identify a subset of the general population with a higher prevalence of traditional cardiovascular risk factors.[15]

The objectives of this study were to (1) estimate the prevalence of subclinical coronary atherosclerosis, defined by

From the Departments of Radiology (H.L., S.L., E.K.F.), Medicine (R.M., G.G., J.C.K., S.L.), Psychiatry (G.T., S.L.), and Pathology (T.K., J.L., S.C., S.L.), Johns Hopkins School of Medicine, Baltimore, MD; Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (D.D.C., S.L.).

Correspondence to: Shenghan Lai, MD, Johns Hopkins School of Medicine, 600 N Wolfe St, Pathology #301, Baltimore, MD 21287. E-mail: slai@jhmi.edu

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coronary artery calcium (CAC), coronary stenosis, noncalcified plaque, calcified plaque, and significant coronary stenosis (>50% in diameter) in African-American (AA) men and women with and without HIV, (2) examine whether HIV infection itself was associated with subclinical atherosclerosis in this population, and (3) assess the association of cocaine addiction and duration of ART therapy with subclinical coronary atherosclerosis in HIV-infected AAs.

Methods

Study Design and Participants

Between June 2004 and February 2015, 1429 AA men and women with and without HIV infection in Baltimore, Maryland, were consecutively enrolled in an observational study investigating the effects of HIV infection, exposure to ART, and cocaine use on subclinical CAD, defined by the presence of CAC detected by noncontrast CT and/or coronary plaque detected by contrast-enhanced coronary CT angiography (CCTA). Among these 1429 subjects, 1257 (88.0%) completed a contrast-enhanced CCTA.

The HIV-infected AAs were recruited from the Johns Hopkins Adult HIV clinic. The HIV-uninfected AAs were recruited from the eastern part of Baltimore City, where the majority of HIV-infected participants reside.

Inclusion criteria were (1) age ≥21 years; (2) HIV-infected and HIV-uninfected. HIV infection, which was determined by ELISA and confirmed by Western blot test (all participants were tested for HIV); (3) chronic cocaine users and noncocaine users. Chronic cocaine use was defined as use by any route for at least 6 months, administered at least 4 times/month. Less-frequent users (fewer than 4 times/month, or <6 consecutive months) were excluded from the study. Noncocaine users were defined as never using cocaine or no use in the past 5 years or longer. Cocaine users could also use other drugs such as opiates, benzodiazepines, methamphetamine, or alcohol; and (4) AA race, which was self-designated. Exclusion criteria were (1) any evidence of clinical CAD or any history of or current symptoms or diagnoses related to cardiovascular disease; (2) history of serious physical disease or current physical disease, including chronic obstructive pulmonary disease; (3) pregnancy; (4) chronic kidney disease with an estimated glomerular filtration rate (eGFR) of <60 mL/minute per 1.73 m^2; and (5) contraindication to CT scans, including a history of contrast allergy.

The Committee on Human Research at the Johns Hopkins School of Medicine (Baltimore, MD) approved the study protocol, and all study participants provided written informed consent. All procedures used in this study were in accord with institutional guidelines.

Procedures

Interview, medical chart review, physical and laboratory examinations

During the baseline visit, study participants underwent a detailed interview to obtain information about sociodemographic characteristics, medical history, risk behaviors, including alcohol consumption, drug use, and cigarette smoking, and other medications used. For HIV-infected participants, detailed information about HIV-related risk factors, duration of known HIV infection, and medications, including ART use, was also collected. A medical chart review was used to confirm the information on medical history and medications provided by the study participants. A physical examination was performed and vital signs were recorded. Routine clinical laboratory blood chemistry tests were conducted. The following laboratory tests were performed at baseline: total cholesterol; triglycerides; high-density lipoprotein (HDL); low-density lipoprotein (LDL); glucose; and inflammation markers, including high-sensitivity CRP (hsCRP).

Blood pressure measurement

Sitting systolic and diastolic blood pressures (SBP and DBP) were measured twice with a standard mercury sphygmomanometer after a nurse at the clinic measured the study participant's arm circumference and applied a correctly sized cuff. The participant sat quietly for 5 minutes before the nurse obtained the SBP and DBP. A second measurement was obtained 3 minutes later, and the average of the 2 readings is reported. Hypertension was defined as SBP >140 mm Hg and/or DBP >90 mm Hg. Antihypertensive medication use was based on self-report of prescribed medications and verified by medical records.

Creatinine-based eGFR

The eGFR is calculated using isotope dilution mass spectrometry–traceable serum creatinine measurements and the patient's age (18 years and older), sex, and race (African American vs non-African American) according to the Chronic Kidney Disease Epidemiology Collaboration equation.[16]

Body Mass Index

Body mass index (BMI) was calculated as weight (in kilograms) over height squared (in meters).

CAC and contrast-enhanced CT angiography with Siemens MDCT scanners

Imaging was performed for participants using a Sensation 64-slice Cardiac scanner (Siemens Medical Solutions, Erlangen, Germany) from May 2004 through June 2009 and a Siemens

128-slice dual-source CT scanner (Somatom Definition FLASH; Siemens Healthcare, Forchheim, Germany) from July 2009 through 2015. The CT scan procedures for the Sensation 64-slice Cardiac scanner were described previously,[13] and the procedures for the 128-slice scanner were as follows.

The participants' studies were performed at the Johns Hopkins Outpatient Center. An 18 g IV was placed in the antecubital fossa and the participant was then brought to the scanner. After a mini test bolus scan to optimize the acquisition timing for the patient (10-cc bolus of contrast and up to 10 low-dose CT slices), the study was performed. The scan parameters were 100 to 120 kVp (depending on the patient's size), image quality reference millamperage of 320 (using Care Dose four-dimensional software to minimize radiation dose), rotation time of 0.28 seconds, collimation of 128×0.6 mm, and average acquisition time of <5 seconds. Scan data were reconstructed with 0.75-mm thickness at 0.5-mm reconstruction spacing using a B26ASA and B30f reconstruction algorithm. Multiphase images were generated across the electrocardiogram pulsing range every 5% to 10% of the R-R interval. Iterative reconstructions were used to optimize image quality. The scan protocol used between 80 and 100 mL of an iso-osmolar contrast agent (Vispaque-320; GE Medical Systems, GE Healthcare Ireland, Cork, Ireland) injected at 5 to 6 cc/s with the test bolus data used to calculate the peak contrast enhancement to determine correct scan delay. All image data were then transferred to a dedicated workstation where image analysis was performed using a combination of axial images, multiplanar reconstruction, and three-dimensional (3D) mapping. Specific software programs that were used included InSpace and Circulation on a Siemens MMW workstation as well as data analysis on an Rcadia cardiac analysis workstation. All images were interpreted by a board-certified radiologist with additional board certification in cardiac CT interpretation.

A noncontrast CT scan was performed to determine the CAC score. CAC score, volume, and mass were measured on a workstation (Leonardo, Syngo; Siemens Medical Solutions, Malvern, PA). The presence of CAC was defined as CAC score >0 based on the Agatston scoring method. Regions of interest were placed over each of the coronary arteries with a threshold for pixels of >130 HU for determining calcified plaque. Coronary vessels were assessed for patency and stenoses using 3D visualization tools after the axial images were reviewed for determination of anatomy, quality of the study, and appearance of the vessels. One reviewer (E.K.F), blinded to the participants' risk factor profiles, independently evaluated the contrast-enhanced computed tomography angiography (CTA) scans. The coronary artery tree was segmented according to the modified American Heart Association (AHA) classification, and the segments were investigated for plaque and luminal narrowing. Calcified plaque was defined as a structure ≥1 mm^2 in size with attenuation >130 HU visualized separately from the intravascular lumen, identified in at least 2 independent planes. Noncalcified plaque was defined as a low-density area ≥1 mm^2 in size and with a CT density ≤130 HU, located within the vessel wall. Partially calcified plaques were categorized into noncalcified plaques. Significant stenosis was defined as >50% diameter stenosis.

Definitions of measures of subclinical CAD

Significant coronary stenosis was defined as >50% diameter stenosis, diagnosed by CCTA. Subclinical CAD was defined by the presence of CAC detected by noncontrast CT and/or coronary plaque detected by CCTA.

Statistical Analysis

Statistical analysis was performed with SAS software (version 9.3; SAS Institute, Cary, NC). All continuous parameters were summarized by medians with interquartile ranges (IQRs), and all categorical parameters were summarized as proportions. To compare between-group differences in demographic and clinical characteristics, lipid profiles, and other factors, the nonparametric Wilcoxon rank-sum test was used for continuous variables and the chi-square test was employed for categorical variables.

To explore associations between HIV infection and subclinical atherosclerosis, several CT parameters were used in the analyses: (1) CAC; (2) any coronary stenosis; (3) noncalcified plaque; (4) calcified plaque; (5) significant coronary plaque; and (6) subclinical CAD. Poisson regression with robust variance was used to examine associations between HIV and the above-mentioned parameters.[17]

Univariate Poisson regression was used to estimate crude prevalence ratios (PRs), and multivariate Poisson regression was used to adjust for the potential confounding factors. Results presented are analyses performed according to 3 levels of adjustments: (1) an unadjusted analysis; (2) an analysis adjusted for cardiovascular risk score assessed by the 2013 American College of Cardiology (ACC)/AHA Guidelines.[18] This cardiovascular risk score is calculated using age, sex, race (white vs African American), total cholesterol, HDL, treated and untreated SBP, current cigarette smoking, and diabetes; and (3) an analysis adjusted for propensity score. Propensity scores were derived from the predicted probability of HIV serostatus (the outcome variable) estimated in a logistic regression model that contained all the covariates listed in Table 1, including age, sex, family history of CAD, cigarette smoking, number of cigarettes smoked per day, year of cigarette smoking, chronic cocaine use, alcohol consumption, hypertension, diabetes, BMI, SBP, DBP, high-sensitivity C-reactive protein (hsCRP), hsCRP ≥2 mg/dL, glucose, total cholesterol, LDL, HDL, triglycerides, eGFR, Framingham risk

Table 1. Characteristics of 1429 African-American Study Participants in Baltimore, Maryland, by HIV Status*

Characteristic	All (N=1429)	HIV− (N=476)	HIV+ (N=953)	*P* Value
Age, y	45 (40–50)	44 (38–48)	46 (41–51)	<0.0001
Male sex (%)	60.3	56.7	62.0	0.054
Family history of CAD (%)	22.9	20.4	24.1	0.11
Cigarette smoking (%)				0.14
Never	16.3	15.5	16.6	
Current	68.7	71.9	67.2	
Former	15.0	12.6	16.2	
No. of cigarettes smoked per day	6 (3–10)	7 (2–10)	6 (3–10)	0.99
Years of cigarette smoking	22 (10–31)	21 (0–30)	23 (10–31)	0.07
Chronic cocaine use (%)	51.6	62.2	46.3	<0.0001
Years of cocaine use	0 (0–15)	5 (0–15)	0 (0–14)	<0.0001
Alcohol use (%)	87.4	90.3	85.9	0.018
Hypertension (%)	29.1	19.8	33.8	<0.0001
Diabetes (%)	6.9	4.8	8.0	0.027
BMI, kg/m^2	25.7 (22.4–30.0)	26.2 (22.9–30.7)	25.3 (22.2–29.5)	0.004
Systolic BP, mm Hg	118 (109–128)	118 (109–128)	118 (108–129)	0.91
Diastolic BP, mm Hg	74 (67–82)	76 (69–83)	73 (67–82)	0.02
hsCRP, mg/dL	1.7 (0.6–4.6)	1.6 (0.6–4.5)	1.7 (0.6–4.7)	0.77
hsCRP ≥2, mg/mL (%)	44.9	44.1	45.2	0.69
Glucose, mg/dL	86 (79–93)	86 (79–93)	86 (78–94)	0.99
Total cholesterol, mg/dL	167 (144–195)	176 (152–201)	163 (140–191)	<0.0001
LDL-C, mg/dL	89 (69–111)	98 (78–119)	86 (66–107)	<0.0001
HDL-C, mg/dL	52 (41–64)	56 (46–69)	50 (39–61)	<0.0001
Triglycerides, mg/dL	99 (68–144)	80 (59–117)	109 (77–156)	<0.0001
eGFR, mL/min per 1.73 m^2	103 (87–119)	112 (92–123)	102 (85–118)	0.0001
Framingham risk	4 (27)	3 (2–6)	4 (2–7)	<0.0001
Framingham score <10 (%)	85.2	90.1	82.8	0.0002
2013 ACC/AHA risk (%)	4.4 (1.5–7.8)	3.4 (1.0–6.2)	5.1 (1.8–8.6)	<0.0001
New ACC/AHA low risk (%)	73.1	83.2	68.1	<0.0001
Year of enrollment (%)				<0.0001
≤2006	26.7	47.5	16.4	
2007–2008	24.8	38.2	18.2	
2009–2010	44.2	5.0	63.7	
>2010	4.3	9.2	1.8	
HIV-related clinical factors				
Years since HIV was diagnosed			12.0 (5.8–17.8)	
CD4 count nadir, cells/mm^3			216 (73–351)	
CD4 count at CTA, cells/mm^3			401 (234–598)	
First HIV RNA, copies/mL			1644 (202–34 298)	
HIV RNA at CTA, copies/mL			51 (48–2674)	
HIV RNA <50 copies/mL (%) at CTA			83.1	
HAART use (%)			79.1	

Continued

Table 1. Continued

Characteristic	All (N=1429)	HIV− (N=476)	HIV+ (N=953)	*P* Value
NRTI use (%)			73.7	
NNRTI use (%)			34.2	
PI use (%)			59.4	
Months of ART use			37 (8–90)	
Months of NRTI use			29 (3–72)	
Months of NNRTI use			0 (0–16)	
Months of PI use			12 (0–60)	

2013 ACC/AHA risk indicates cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk[18]; ACC indicates American College of Cardiology; AHA, American Heart Association; ART, antiretroviral therapy; BMI, body mass index (kg/m^2); BP, blood pressure; CAD, coronary artery disease; CD4 count nadir, the lowest CD4 count since HIV diagnosis; CTA, computed tomography angiography; eGFR, estimated glomerular filtration rate; Framingham risk, Framingham risk score; glucose, fasting glucose; HAART, highly active antiretroviral therapy; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; new ACC/AHA low risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk <7.5%[18]; NNRTI, non-nucleoside reverse-transcriptase inhibitors; NRTI, nucleoside reverse-transcriptase inhibitors; PI, protease inhibitors.

*Median (interquartile range) for continuous variables, proportion (%) for categorical variables.

score, Framingham risk score <10%, the cardiovascular risk, defined by the 2013 ACC/AHA guidelines, the cardiovascular risk, defined by the 2013 ACC/AHA guidelines <7.5%, year of enrollment, year of alcohol consumption, other illicit drugs (such as opiates, benzodiazepines, and methamphetamine), frequency of cocaine use, and their second-order interaction terms.[19–21] The rationale for use of propensity score was to minimize the differences in potential confounding factors (such as cardiovascular risk factors listed in Table 1) between those HIV uninfected and those HIV infected. To estimate the effect of HIV infection per se on subclinical atherosclerosis, systematic differences in characteristics between these 2 groups must be accounted for.

To examine whether duration of ART use is associated with the presence of subclinical atherosclerosis, stratified Poisson regression analyses (by duration of ART, categorized as ART naïve, ART use <36 months, and ART use ≥36 months) were also performed as described above. The 36 months was selected because it represented the median duration of ART use in the participant population. The *P* values reported are 2-sided. $P<0.05$ indicated statistical significance.

Results

A total of 1429 participants had noncontrast CT scan results and 1257 (88.0%) had contrast-enhanced coronary CTA results for the analysis. The demographic, behavioral, and clinical characteristics of all participants and HIV-related clinical factors of HIV-infected participants are presented in Table 1. Of the 1429 in this study, 861 (60.3%) were men and 953 (68.7%) were infected with HIV (Table 1). Median age was 45 years (IQR, 40–50). Approximately 73% of study participants were at low cardiovascular risk based on the 2013 ACC/AHA Guideline.[18]

Compared to HIV uninfected, those with HIV infection were significantly older ($P<0.0001$). Alcohol use was significantly more common in HIV uninfected than that in HIV infected ($P=0.018$). Cocaine use was also significantly more common ($P<0.0001$), and duration of cocaine use significantly longer ($P<0.0001$) in HIV uninfected than in HIV infected. Hypertension and diabetes were significantly more prevalent in HIV infected than HIV uninfected ($P<0.0001$ and $P=0.027$, respectively). Compared to HIV uninfected, those with HIV infection had significantly lower BMI ($P=0.004$), DBP ($P=0.02$), total cholesterol ($P<0.0001$), LDL ($P<0.0001$), HDL ($P<0.0001$), and eGFR ($P=0.0001$) and significantly higher triglycerides ($P<0.0001$), Framingham risk score ($P<0.0001$), and 2013 ACC/AHA cardiovascular risk score based on the 2013 ACC/AHA Guideline[18] ($P<0.0001$).

Prevalence of Subclinical Coronary Atherosclerosis by HIV Serostatus, and Cardiovascular Risk Profile Quintile

Overall prevalence of subclinical CAD was 32.5% (95% CI, 30.0–34.9%). Prevalences of all the subclinical coronary atherosclerosis parameters in HIV infected were slightly higher than those in HIV uninfected except for significant stenosis; however, none of these differences were statistically significant (Figure 1). Prevalences of all the subclinical coronary atherosclerosis parameters by the 2013 ACC/AHA cardiovascular risk profile quintile are presented in Figure 2. Prevalences of all the subclinical coronary atherosclerosis parameters increased with the 2013 ACC/AHA cardiovascular risk profile quintile (Figure 2); however, the differences in prevalences of all the subclinical coronary atherosclerosis parameters between HIV infected and uninfected in each

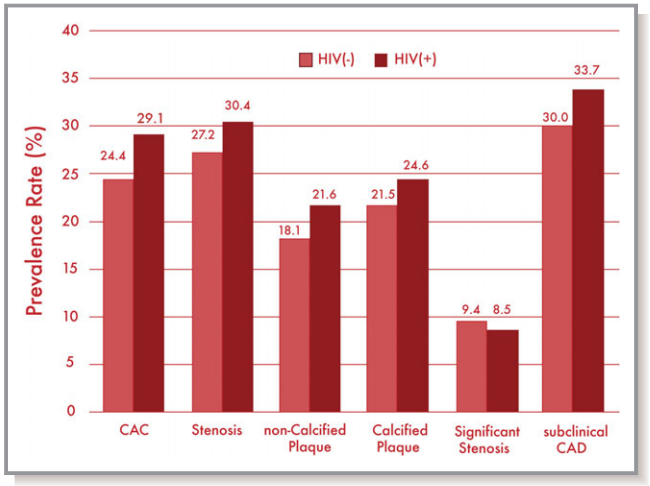

Figure 1. Prevalences of subclinical CAD by HIV serostatus. Prevalences of CAC were 24.4% in HIV uninfected and 29.1% in HIV infected (P=0.06). Prevalences of any coronary stenosis were 27.2% in HIV uninfected and 30.4% in HIV infected (P=0.24). Prevalences of noncalcified plaque were 18.1% in HIV uninfected and 21.6% in HIV infected (P=0.13). Prevalences of calcified plaque were 21.5% in HIV uninfected and 24.6% in HIV infected (P=0.22). Prevalences of significant stenosis were 9.4% in HIV uninfected and 8.5% in HIV infected (P=0.61). Prevalences of subclinical CAD were 30.0% in HIV uninfected and 33.7% in HIV infected (P=0.17). CAC indicates coronary artery calcium, stenosis, any coronary stenosis; subclinical CAD, either presence of CAC and/or any coronary stenosis; HIV+, HIV-infected; HIV−, HIV-uninfected.

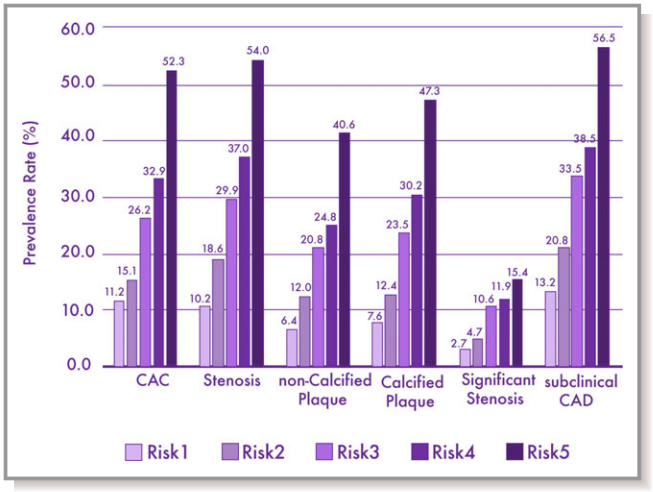

Figure 2. Unadjusted prevalence estimates of subclinical CAD by the 2013 ACC/AHA cardiovascular risk profile quintile. Prevalences of all the subclinical atherosclerosis parameters increased with the 2013 ACC/AHA cardiovascular risk profile quintile (linear trend, P<0.007 for all the parameters). ACC indicates American College of Cardiology; AHA, American Heart Association; CAC, coronary artery calcium, stenosis, any coronary stenosis; subclinical CAD, either presence of CAC and/or any coronary stenosis. Risk1, risk2, risk3, risk4, and risk5: the first quintile, second quintile, third quintile, fourth quintile, and fifth quintile.

quintile of the 2013 ACC/AHA cardiovascular risk profile were not significant (Figure 2).

Overall Associations Between HIV Serostatus and Subclinical Coronary Atherosclerosis

The results of unadjusted Poisson regression analyses relating subclinical coronary atherosclerosis to HIV infection indicated that HIV infection was significantly associated with the presence of CAC (P=0.007), any coronary plaque (P=0.03), calcified plaque (P=0.014), and subclinical CAD (P=0.03) in those who never used cocaine (Table 2). However, when adjusted for the ACC/AHA risk or when adjusted for the propensity score for HIV serostatus, all associations between HIV serostatus and all subclinical atherosclerosis parameters were not statistically significant in all participants or any subset of them (Table 2).

Modification of the Overall Associations Between HIV Serostatus and Subclinical Coronary Atherosclerosis by Duration of ART Use in HIV-Infected Participants

On univariable Poisson regression analyses, there were trends suggesting that compared to HIV uninfected, those who were HIV infected and ART naïve were at a lower risk for presence of CAC, noncalcified plaque, calcified plaque, >50% coronary stenosis, and subclinical CAD, but these associations were not statistically significant. However, multivariable Poisson regression analysis showed that after adjustment for propensity score for HIV infection, those who were HIV infected and ART naïve were at significantly lower risk for the presence of any coronary stenosis (the propensity score–adjusted PR, 0.62; 95% CI, 0.41, 0.94; P value, 0.026), noncalcified plaque (the propensity score–adjusted PR, 0.56; 95% CI, 0.33, 0.94; P value, 0.029), and subclinical CAD (the propensity score–adjusted PR, 0.68; 95% CI, 0.47, 0.99; P value, 0.046), compared to HIV uninfected (Table 3 and Figure 3).

Both uni- and multivariable Poisson regression analyses indicated that those who were HIV infected and had used ART for <36 months were not at a higher risk for all CT outcome parameters, compared to HIV uninfected (Table 3 and Figure 3).

According to univariable Poisson regression analyses, those who were HIV infected and had used ART for ≥36 months were at significantly higher risk for the presence of CAC (P=0.007), any coronary stenosis (P=0.007), noncalcified plaque (P=0.009), calcified plaque (P=0.021), and subclinical CAD (P=0.006), compared to HIV uninfected. Multivariable Poisson regression analysis showed that after controlling for propensity score for HIV infection, those who were HIV infected and had used ART for ≥36 months were at

Table 2. Associations Between Presence of Subclinical Atherosclerosis and HIV Serostatus

Outcome Variable	Unadjusted		Adjusted for HIV and ACC/AHA Risk*		Adjusted for Propensity Score†	
	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value
All subjects						
Presence of CAC (N=1429)	1.19 (0.96, 1.48)	0.11	1.06 (0.85, 1.32)	0.63	1.02 (0.80, 1.31)	0.84
Contrast-enhanced CTA (N=1257)						
Any coronary plaque	1.12 (0.93, 1.34)	0.24	1.01 (0.84, 1.21)	0.92	1.05 (0.84, 1.32)	0.67
Noncalcified plaque	1.19 (0.95, 1.51)	0.14	1.08 (0.85, 1.37)	0.52	1.06 (0.78, 1.43)	0.72
Calcified plaque	1.14 (0.92, 1.41)	0.22	1.02 (0.83, 1.26)	0.84	1.01 (0.77, 1.33)	0.92
Coronary stenosis (>50%)	0.91 (0.63, 1.31)	0.61	0.86 (0.59, 1.24)	0.42	1.12 (0.70, 1.78)	0.64
Subclinical CAD	1.12 (0.95, 1.32)	0.17	1.01 (0.86, 1.19)	0.94	1.04 (0.84, 1.28)	0.72
Male subjects						
Presence of CAC (N=861)	1.20 (0.96, 1.49)	0.11	1.03 (0.82, 1.28)	0.81	1.17 (0.88, 1.56)	0.27
Contrast-enhanced CTA (N=754)						
Any coronary plaque	1.11 (0.90, 1.37)	0.34	0.99 (0.80, 1.22)	0.89	1.18 (0.90, 1.54)	0.23
Noncalcified plaque	1.21 (0.92, 1.60)	0.18	1.06 (0.80, 1.40)	0.70	1.23 (0.86, 1.76)	0.27
Calcified plaque	1.09 (0.85, 1.39)	0.51	0.95 (0.74, 1.22)	0.70	1.10 (0.80, 1.52)	0.55
Coronary stenosis (>50%)	0.91 (0.59, 1.39)	0.66	0.86 (0.56, 1.33)	0.50	1.37 (0.81, 2.32)	0.24
Subclinical CAD	1.14 (0.94, 1.38)	0.19	1.00 (0.82, 1.21)	0.98	1.18 (0.92, 1.51)	0.19
Female subjects						
Presence of CAC (N=568)	1.09 (0.77, 1.55)	0.61	1.00 (0.71, 1.41)	0.99	0.76 (0.48, 1.20)	0.24
Contrast-enhanced CTA (N=503)						
Any coronary plaque	1.05 (0.75, 1.47)	0.79	0.96 (0.68, 1.35)	0.82	0.82 (0.54, 1.24)	0.37
Noncalcified plaque	1.08 (0.70, 1.66)	0.72	1.00 (0.65, 1.54)	0.99	0.75 (0.44, 1.29)	0.30
Calcified plaque	1.19 (0.79, 1.78)	0.40	1.07 (0.71, 1.60)	0.75	0.83 (0.50, 1.38)	0.48
Coronary stenosis (>50%)	0.83 (0.42, 1.64)	0.59	0.80 (0.40, 1.60)	0.52	0.68 (0.26, 1.75)	0.42
Subclinical CAD	1.01 (0.74, 1.37)	0.95	0.93 (0.69, 1.26)	0.65	0.79 (0.53, 1.18)	0.25
Subjects who never used cocaine						
Presence of CAC (N=692)	1.62 (1.14, 6.80)	0.007	1.32 (0.93, 1.88)	0.12	1.15 (0.73, 1.80)	0.55
Contrast-enhanced CTA (N=596)						
Any coronary plaque	1.45 (1.04, 2.02)	0.03	1.22 (0.88, 1.71)	0.24	1.15 (0.76, 1.76)	0.50
Noncalcified plaque	1.22 (0.83, 1.80)	0.30	1.04 (0.71, 1.53)	0.84	0.83 (0.49, 1.39)	0.48
Calcified plaque	1.66 (1.11, 2.48)	0.014	1.40 (0.93, 2.09)	0.10	1.23 (0.73, 2.08)	0.44
Coronary stenosis (>50%)	1.02 (0.53, 1.95)	0.95	0.88 (0.45, 1.72)	0.71	1.07 (0.45, 2.52)	0.88
Subclinical CAD	1.38 (1.02, 1.86)	0.03	1.14 (0.68, 1.54)	0.38	1.03 (0.70, 1.51)	0.89
Subjects who used cocaine						
Presence of CAC (N=737)	1.06 (0.81, 1.39)	0.68	0.99 (0.75, 1.30)	0.95	0.99 (0.74, 1.33)	0.96
Contrast-enhanced CTA (N=661)						
Any coronary plaque	1.02 (0.81, 1.27)	0.87	0.96 (0.77, 1.20)	0.75	1.02 (0.78, 1.34)	0.88
Noncalcified plaque	1.22 (0.91, 1.65)	0.19	1.15 (0.85, 1.55)	0.37	1.22 (0.85, 1.76)	0.27
Calcified plaque	1.00 (0.77, 1.29)	0.97	0.93 (0.72, 1.20)	0.56	0.95 (0.68, 1.31)	0.73
Coronary stenosis (>50%)	0.95 (0.61, 1.47)	0.80	0.93 (0.60, 1.46)	0.76	1.15 (0.66, 2.07)	0.62
Subclinical CAD	1.05 (0.87, 1.29)	0.61	1.00 (0.82, 1.21)	0.98	1.07 (0.83, 1.37)	0.87

ACC indicates American College of Cardiology; AHA, American Heart Association; CAC, coronary artery calcium; subclinical CAD, either presence of CAC and/or any coronary stenosis; CTA, computed tomography angiography; PR, prevalence ratio.

*Adjusted for cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.

†Adjusted for propensity score.

Table 3. Associations Between the Presence of Subclinical Coronary Atherosclerosis and HIV Serostatus by Duration of ART Use (All Study Participants Included, HIV Uninfected as the Reference Group)

Outcome Variable	Unadjusted		Adjusted for ACC/AHA Risk*		Adjusted for Propensity Score†	
	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value
I. Comparing those HIV infected ART naïve with HIV uninfected						
All subjects						
Presence of CAC (N=675)	0.80 (0.56, 1.16)	0.24	0.69 (0.48, 0.99)	0.046	0.70 (0.46, 1.08)	0.11
Contrast-enhanced CTA (N=647)						
Any coronary plaque	0.77 (0.56, 1.06)	0.11	0.71 (0.52, 0.97)	0.03	0.62 (0.41, 0.94)	0.026
Noncalcified plaque	0.81 (0.54, 1.22)	0.31	0.75 (0.51, 1.11)	0.15	0.56 (0.33, 0.94)	0.029
Calcified plaque	0.76 (0.52, 1.11)	0.16	0.70 (0.49, 1.01)	0.058	0.62 (0.38, 1.01)	0.056
Coronary stenosis (>50%)	0.60 (0.31, 1.17)	0.14	0.57 (0.29, 1.11)	0.097	0.69 (0.30, 1.57)	0.38
Subclinical CAD	0.82 (0.62, 1.08)	0.16	0.72 (0.55, 0.94)	0.016	0.68 (0.47, 0.99)	0.046
II. Comparing those HIV infected and ART exposure <36 months with HIV uninfected						
All subjects						
Presence of CAC (N=750)	1.14 (0.85, 1.52)	0.38	1.02 (0.76, 1.38)	0.88	1.31 (0.91, 1.87)	0.14
Contrast-enhanced CTA (N=698)						
Any coronary plaque	1.05 (0.81, 1.35)	0.72	0.94 (0.73, 1.22)	0.66	1.18 (0.84, 1.66)	0.33
Noncalcified plaque	1.14 (0.83, 1.57)	0.42	1.02 (0.73, 1.42)	0.90	1.18 (0.84, 1.66)	0.33
Calcified plaque	1.14 (0.86, 1.52)	0.36	1.01 (0.75, 1.36)	0.95	1.23 (0.83, 1.82)	0.29
Coronary stenosis (>50%)	1.08 (0.67, 1.74)	0.76	1.03 (0.63, 1.69)	0.90	1.55 (0.82, 2.93)	0.18
Subclinical CAD	1.06 (0.85, 1.32)	0.62	0.96 (0.77, 1.21)	0.74	1.24 (0.91, 1.70)	0.17
III. Comparing those HIV infected and ART exposure ≥36 months with HIV uninfected						
All subjects						
Presence of CAC (N=956)	1.38 (1.09, 1.76)	0.007	1.17 (0.92, 1.50)	0.21	1.11 (0.82, 1.52)	0.50
Contrast-enhanced CTA (N=852)						
Any coronary plaque	1.32 (1.08, 1.61)	0.007	1.15 (0.94, 1.41)	0.18	1.35 (1.02, 1.79)	0.036
Noncalcified plaque	1.41 (1.09, 1.82)	0.009	1.23 (0.95, 1.61)	0.12	1.34 (0.91, 1.99)	0.14
Calcified plaque	1.32 (1.04, 1.67)	0.021	1.12 (0.88, 1.43)	0.34	1.17 (0.83, 1.66)	0.36
Coronary stenosis (>50%)	0.95 (0.62, 1.46)	0.82	0.86 (0.55, 1.34)	0.50	1.30 (0.71, 2.37)	0.39
Subclinical CAD	1.28 (1.07, 1.53)	0.006	1.11 (0.93, 1.33)	0.25	1.24 (0.95, 1.62)	0.12

ACC indicates American College of Cardiology; AHA, American Heart Association; ART, antiretroviral therapy; CAC, coronary artery calcium; subclinical CAD, either presence of CAC and/or any coronary stenosis; CTA, computed tomography angiography; PR, prevalence ratio.
*Adjusted for cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.
†Adjusted for propensity score.

significantly higher risk for the presence of any coronary stenosis (the propensity score–adjusted PR, 1.35; 95% CI, 1.02, 1.79; *P* value, 0.036), compared to HIV uninfected (Table 3 and Figure 3).

Associations Between Duration of ART Use and Subclinical Coronary Atherosclerosis in HIV-Infected Participants

Associations between duration of ART use and subclinical coronary atherosclerosis in HIV infected are presented in Table 4. Both uni- and multivariable Poisson regression analyses indicated that compared to those who were ART naïve, those who had used ART <36 months were not at significantly higher risk of any CT outcome parameter.

However, univariable Poisson regression analyses indicated that compared to those who were ART naïve, those who had used ART ≥36 months were at significantly higher risk for the presence of CAC, any coronary stenosis, noncalcified plaque, calcified plaque, and subclinical CAD. Multivariable Poisson regression analyses showed that compared to those

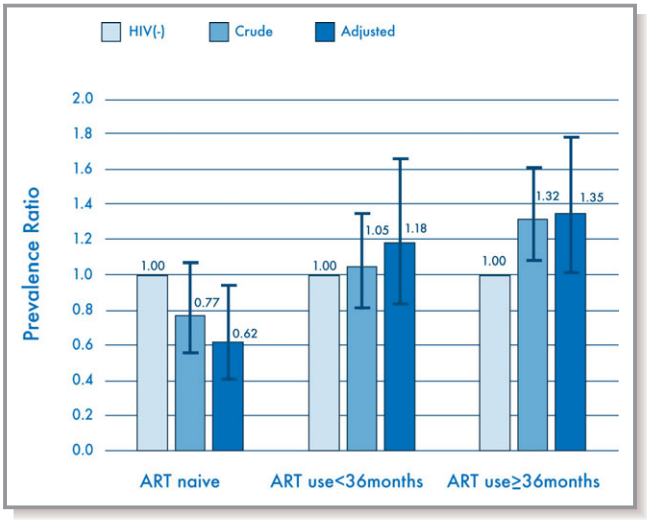

Figure 3. Associations between HIV infection and presence of coronary stenosis by duration of ART use. On univariable Poisson regression analyses, there were trends suggesting that compared to HIV uninfected, those who were HIV infected and had been ART naïve were at a lower risk for the presence of CAC, noncalcified plaque, calcified plaque, >50% coronary stenosis, and subclinical CAD, but these associations were not statistically significant. However, multivariable Poisson regression analysis showed that after adjustment for propensity score for HIV infection, those who were HIV infected and had been ART naïve were at significantly lower risk for presence of any coronary stenosis (the propensity score–adjusted PR, 0.62; 95% CI, 0.41, 0.94; *P* value, 0.026), noncalcified plaque (the propensity score–adjusted PR, 0.56; 95% CI, 0.33, 0.94; *P* value, 0.029), and subclinical CAD (the propensity score–adjusted PR, 0.68; 95% CI, 0.47, 0.99; *P* value, 0.046), compared to HIV uninfected. Both uni- and multivariable Poisson regression analyses indicated that those who were HIV infected and had used ART for <36 months were not at a higher risk for all CT outcome parameters, compared to HIV uninfected. According to univariable Poisson regression analysis, those who were HIV infected and had used ART for ≥36 months were at significantly higher risk for presence of CAC (*P*=0.007), any coronary stenosis (*P*=0.007), noncalcified plaque (*P*=0.009), calcified plaque (*P*=0.021), and subclinical CAD (*P*=0.006), compared to HIV uninfected. Multivariable Poisson regression analysis showed that after controlling for propensity score for HIV infection, those who were HIV infected and had used ART for ≥36 months were at significantly higher risk for presence of any coronary stenosis (the propensity score–adjusted PR, 1.35; 95% CI, 1.02, 1.79; *P* value, 0.036), compared to HIV uninfected. ART indicates antiretroviral therapy; CAC, coronary artery calcium, stenosis, any coronary stenosis; subclinical CAD, either presence of CAC and/or any coronary stenosis; CT, computed tomography; PR, prevalence ratio.

who were ART naïve, those who had used ART ≥36 months were at significantly higher risk for the presence of CAC (the propensity score–adjusted PR, 1.45; 95% CI, 1.04, 2.03; *P* value, 0.028), any coronary stenosis (the propensity score–adjusted PR, 1.49; 95% CI, 1.04, 2.12; *P* value, 0.03), noncalcified plaque (the propensity score–adjusted PR, 1.56; 95% CI, 1.01, 2.44; *P* value, 0.049), and subclinical CAD (the propensity score–adjusted PR, 1.38; 95% CI, 1.03, 1.84; *P* value, 0.03; Table 4).

Associations Between Cocaine Use and Subclinical Coronary Atherosclerosis

Univariable Poisson regression analyses indicated that compared to those who had never used cocaine, those who had used cocaine chronically were at significantly higher risk for the presence of any coronary stenosis, calcified plaque, >50% coronary stenosis, and subclinical CAD. Multivariable Poisson regression analyses after controlling for propensity score for cocaine use showed that compared to those who had never used cocaine, those who had used cocaine chronically were at significantly higher risk for the presence of CAC (the propensity score–adjusted PR, 1.26; 95% CI, 1.05, 1.52; *P* value, 0.013), any coronary stenosis (the propensity score–adjusted PR, 1.30; 95% CI, 1.08, 1.57; *P* value, 0.006), calcified plaque (the propensity score–adjusted PR, 1.37; 95% CI, 1.10, 1.71; *P* value, 0.005), and subclinical CAD (the propensity score–adjusted PR, 1.27; 95% CI, 1.08, 1.49; *P* value, 0.004; Table 5).

Effect of Cocaine Use on the Associations Between Long-Term ART Use (≥36 Months) and Subclinical Coronary Atherosclerosis in HIV-Infected Participants

Associations between cocaine use and subclinical coronary atherosclerosis by cocaine use status (never use vs chronic use) are shown in Table 6. By univariable Poisson regression analyses, compared to those who were ART naïve, those who had never used cocaine and had used ART ≥36 months were at significantly higher risk for CAC, coronary stenosis, calcified plaque, and subclinical CAD, whereas chronic cocaine users who had used ART ≥36 months were at significantly higher risk for the presence of CAC, coronary stenosis, noncalcified plaque, calcified plaque, and subclinical CAD. However, after controlling for propensity score, multivariable Poisson regression analyses showed that compared to those who were ART naïve, those who had never used cocaine and had used ART ≥36 months were not at significantly higher risk for any CT outcome variables, whereas chronic cocaine users who had used ART ≥36 months were at significantly higher risk for the presence of coronary stenosis (the propensity score–adjusted PR, 1.87; 95% CI, 1.19, 2.94; *P* value, 0.007), noncalcified plaque (the propensity score–adjusted PR, 2.46; 95% CI, 1.30, 4.66; *P* value, 0.006), and subclinical CAD (the propensity score–adjusted PR, 1.62; 95% CI, 1.17, 2.35; *P* value, 0.011; Table 6).

Table 4. Associations Between Presence of Subclinical Coronary Atherosclerosis and Duration of ART Use in HIV Infected (ART Naïve as the Reference Group)

	ART Use <36 Months						ART Use ≥36 Months					
	Unadjusted		Adjusted for ACC/AHA Risk*		Adjusted for Propensity Score†		Unadjusted		Adjusted for ACC/AHA Risk*		Adjusted for Propensity Score†	
Outcome Variable	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value
All subjects (N=953)												
Presence of CAC	1.42 (0.96, 2.08)	0.08	1.35 (0.92, 1.99)	0.12	1.34 (0.93, 1.91)	0.11	1.72 (1.21, 2.44)	0.002	1.61 (1.13, 2.29)	0.008	1.45 (1.04, 2.03)	0.028
Contrast-enhanced CTA (N=787)												
Any coronary plaque	1.36 (0.96, 1.94)	0.11	1.29 (0.91, 1.83)	0.16	1.28 (0.89, 1.85)	0.18	1.72 (1.25, 2.35)	0.0008	1.59 (1.16, 2.17)	0.004	1.49 (1.04, 2.12)	0.03
Noncalcified plaque	1.40 (0.91, 2.17)	0.13	1.32 (0.85, 2.04)	0.22	1.29 (0.83, 2.02)	0.26	1.73 (1.17, 2.57)	0.006	1.61 (1.09, 2.38)	0.016	1.56 (1.01, 2.44)	0.049
Calcified plaque	1.50 (1.01, 2.24)	0.049	1.40 (0.93, 2.09)	0.10	1.38 (0.92, 2.09)	0.12	1.73 (1.20, 2.51)	0.004	1.61 (1.11, 2.31)	0.011	1.50 (1.00, 2.27)	0.052
Coronary stenosis (>50%)	1.79 (0.87, 3.66)	0.11	1.76 (0.86, 3.61)	0.12	1.34 (0.61, 2.92)	0.47	1.58 (0.80, 3.12)	0.19	1.52 (0.77, 3.02)	0.23	1.61 (0.73, 3.54)	0.24
Subclinical CAD	1.29 (0.96, 1.74)	0.10	1.24 (0.93, 1.67)	0.15	1.25 (0.91, 1.71)	0.17	1.57 (1.20, 2.05)	0.001	1.47 (1.14, 1.91)	0.004	1.38 (1.03, 1.84)	0.03

ACC indicates American College of Cardiology; AHA, American Heart Association; ART, antiretroviral therapy; CAC, coronary artery calcium; subclinical CAD, either presence of CAC and/or any coronary stenosis; CTA, computed tomography angiography; PR, prevalence ratio.

*Adjusted for cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.

†Adjusted for propensity score.

Table 5. Associations Between the Presence of Subclinical Coronary Atherosclerosis and Cocaine Use in All Study Participants

Outcome Variable	Unadjusted		Adjusted for HIV and ACC/AHA Risk*		Adjusted for Propensity Score†	
	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value
All subjects						
Presence of CAC (N=1429)	1.18 (0.97, 1.44)	0.10	1.23 (1.01, 1.50)	0.045	1.26 (1.05, 1.52)	0.013
Contrast-enhanced CTA (N=1257)						
Any coronary plaque	1.23 (1.04, 1.47)	0.019	1.26 (1.06, 1.50)	0.01	1.30 (1.08, 1.57)	0.006
Noncalcified plaque	1.13 (0.91, 1.41)	0.27	1.16 (0.92, 1.45)	0.20	1.26 (0.99, 1.59)	0.06
Calcified plaque	1.25 (1.02, 1.54)	0.030	1.27 (1.04, 1.56)	0.021	1.37 (1.10, 1.71)	0.005
Coronary stenosis (>50%)	1.54 (1.06, 2.27)	0.022	1.53 (1.06, 2.23)	0.025	1.34 (0.91, 1.97)	0.64
Subclinical CAD	1.22 (1.05, 1.42)	0.011	1.26 (1.08, 1.46)	0.003	1.27 (1.08, 1.49)	0.004

ACC indicates American College of Cardiology; AHA, American Heart Association; CAC, coronary artery calcium; subclinical CAD, either presence of CAC and/or any coronary stenosis; CTA, computed tomography angiography; PR, prevalence ratio.

*Adjusted for HIV infection and cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.

†Adjusted for propensity score.

Comparisons of Subclinical Atherosclerosis-Associated Factors Between HIV-Uninfected and HIV-Infected ART Naïve Participants

Subclinical atherosclerosis-related characteristics between those who were HIV-uninfected and those who were HIV-infected and ART naïve were compared (Table 7). Compared to HIV uninfected, those who were HIV infected and ART naïve had a significantly higher traditional cardiovascular risk than those without HIV infection, according to Framingham risk score (P=0.02) and the cardiovascular risk assessed by the 2013 ACC/AHA guidelines (P=0.008). Nevertheless, those without HIV infection had used cocaine significantly more commonly (P<0.0001) and had used cocaine significantly longer than those who were HIV infected and ART naïve (P=0.006).

Discussion

The findings of this study demonstrate that (1) cardiovascular risk profile measured by cardiovascular risk score based on the 2013 ACC/AHA Guideline was significantly associated with the presence of subclinical coronary atherosclerosis, (2) cardiovascular risk profiles were significantly worse in HIV-infected than in HIV-uninfected persons, (3) this study did not find any evidence for an independent association between HIV infection and subclinical coronary atherosclerosis when all HIV-infected participants as 1 group were compared with HIV uninfected, (4) duration of ART use in HIV-infected modified the overall association between HIV infection and subclinical coronary atherosclerosis, (5) cocaine use was independently associated with subclinical coronary atherosclerosis, and (6) the magnitude of long-term ART exposure-associated risk depended on cocaine use status.

Our study shows that traditional cardiovascular risk profile was significantly associated with the presence of subclinical atherosclerosis. This finding is consistent with other published data.[15]

Our results also show that traditional cardiovascular risk profiles were worse in the HIV infected than HIV uninfected in this population. Nevertheless, given the limitations of data from observational studies, in which selection bias is not avoidable, we treated traditional cardiovascular risk profile as a covariate because the purpose of this investigation was to examine whether HIV infected per se influenced subclinical coronary atherosclerosis.

Prevalence of subclinical coronary atherosclerosis reported in this study was different from other published data. Lo et al. compared 78 HIV-infected men with 32 HIV-uninfected men with similar demographic and CAD risk factors, and found that the prevalence of coronary atherosclerosis was higher in HIV-infected men than in non-HIV-infected men (59% vs 34%; P=0.02).[10] In previous studies reported by our group, prevalences of any coronary stenosis were similar by HIV status.[6–9,11–13] In Post et al., the prevalence of coronary plaque in men was dramatically higher at 76% (77.6% in HIV infected vs 74.4% in HIV uninfected)[14] than in our current study, where the prevalence in men is 30%.

Unlike our results, which did not find evidence for an independent association between HIV infection and subclinical coronary atherosclerosis, Post et al. found a significant association between HIV infection and coronary plaque (adjusted PR for age, race, CT scanning center, and cohort) was 1.14 (95% CI, 1.05, 1.24; P=0.001).[14] There are several

Table 6. Associations Between Presence of Subclinical Coronary Atherosclerosis and Long-Term ART Use (≥36 Months) in the HIV Infected by Cocaine Use Status (ART Naïve as the Reference Group)

	Never Cocaine Use						Chronic Cocaine Use					
	Unadjusted		Adjusted for ACC/AHA Risk*		Adjusted for Propensity Score†		Unadjusted		Adjusted for ACC/AHA Risk*		Adjusted for Propensity Score†	
Outcome Variable	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value	PR (95% CI)	*P* Value
All subjects (N=679)												
Presence of CAC	1.56 (1.07, 2.27)	0.020	1.39 (0.95, 2.03)	0.09	1.08 (0.87, 1.35)	0.47	1.99 (1.34, 2.91)	0.0006	1.88 (1.27, 2.78)	0.002	1.45 (0.98, 2.15)	0.06
Contrast-enhanced CTA (N=559)												
Any coronary plaque	1.48 (1.05, 2.10)	0.025	1.31 (0.93, 1.85)	0.12	1.13 (0.84, 1.35)	0.60	2.07 (1.48, 2.91)	<0.0001	1.95 (1.40, 2.73)	<0.0001	1.87 (1.19, 2.94)	0.007
Noncalcified plaque	1.41 (0.91, 2.18)	0.12	1.26 (0.81, 1.95)	0.31	1.07 (0.79, 1.45)	0.65	2.22 (1.46, 3.39)	0.0002	2.08 (1.37, 3.17)	0.0006	2.46 (1.30, 4.66)	0.006
Calcified plaque	1.53 (1.03, 2.29)	0.037	1.36 (0.91, 2.03)	0.14	1.17 (0.90, 1.53)	0.25	2.03 (1.36, 3.04)	0.0005	1.90 (1.27, 2.83)	0.002	1.55 (0.95, 2.51)	0.07
Coronary stenosis (>50%)	1.37 (0.65, 2.90)	0.41	1.26 (0.60, 2.71)	0.53	1.44 (0.88, 2.31)	0.15	1.89 (0.88, 4.04)	0.10	1.82 (0.85, 3.92)	0.12	1.35 (0.45, 4.05)	0.60
Subclinical CAD	1.37 (1.02, 1.83)	0.035	1.23 (0.93, 1.64)	0.15	1.04 (0.85, 1.27)	0.67	1.87 (1.40, 2.49)	<0.0001	1.79 (1.35, 2.38)	<0.0001	1.62 (1.17, 2.35)	0.011

ACC indicates American College of Cardiology; AHA, American Heart Association; ART, antiretroviral therapy; CAC, coronary artery calcium; subclinical CAD, either presence of CAC and/or any coronary stenosis; CTA, computed tomography angiography; PR, prevalence ratio.

*Adjusted for cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.

†Adjusted for propensity score.

Table 7. Comparison of Characteristics in HIV Uninfected and HIV Infected but ART-Naïve Study Participants*

Characteristic	HIV Uninfected (N=476)	HIV Infected, ART Naïve (N=199)	*P* Value
Age, y	44 (38–48)	44 (39–49)	0.05
Male sex (%)	56.7	60.3	0.39
Family history of CAD (%)	20.4	24.1	0.28
Cigarette smoking (%)			0.70
Never	15.5	18.0	
Current	71.9	70.4	
Former	12.6	11.6	
No. of cigarettes smoked per day	7 (2–10)	7 (2–10)	0.94
Years of cigarette smoking	21 (0–30)	21 (10–30)	0.76
Chronic cocaine use (%)	62.2	46.3	<0.0001
Years of cocaine use	5 (0–15)	0 (0–14)	0.006
Alcohol use (%)	90.3	85.9	0.09
Hypertension (%)	19.8	31.7	<0.0008
Diabetes (%)	4.8	8.0	0.10
BMI, kg/m^2	26.2 (22.9–30.7)	25.7 (22.9–31.0)	0.58
Systolic BP, mm Hg	118 (109–128)	118 (107–128)	0.65
Diastolic BP, mm Hg	76 (69–83)	73 (66–82)	0.13
hsCRP, mg/dL	1.6 (0.6–4.5)	1.8 (0.6–4.1)	0.86
hsCRP ≥2, mg/mL (%)	44.1	44.2	0.98
Glucose, mg/dL	86 (79–93)	84 (77–92)	0.12
Total cholesterol, mg/dL	176 (152–201)	157 (133–179)	<0.0001
LDL-C, mg/dL	98 (78–119)	87 (66–107)	<0.0001
HDL-C, mg/dL	56 (46–69)	45 (36–56)	<0.0001
Triglycerides, mg/dL	80 (59–117)	101 (72–138)	<0.0001
eGFR, mL/min per 1.73 m^2	112 (92–123)	105 (89–120)	0.08
Framingham risk	3 (2–6)	4 (2–7)	0.02
Framingham score <10 (%)	90.1	86.9	0.22
2013 ACC/AHA risk (%)	3.4 (1.0–6.2)	3.9 (16–7.6)	0.008
New ACC/AHA low risk (%)	83.2	74.9	0.013
Year of enrollment (%)			<0.0001
<2006	47.5	29.1	
2007–2008	38.2	15.6	
2009–2010	5.0	53.3	
>2010	9.2	1.5	

2013 ACC/AHA risk indicates cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk[18]; ACC indicates American College of Cardiology; AHA, American Heart Association; ART, antiretroviral therapy; BMI, body mass index (kg/m^2); BP, blood pressure; CAD, coronary artery disease; CD4 count nadir, the lowest CD4 count since HIV diagnosis; eGFR, estimated glomerular filtration rate; Framingham risk, Framingham risk score; glucose, fasting glucose; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; new ACC/AHA low risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk <7.5%.[18]

*Median (interquartile range) for continuous variables, proportion (%) for categorical variables.

possible explanations for this difference. Probably the most significant difference is that noncalcified plaque in Post et al.[14] was defined as "*any discernible* structure that could be clearly assignable to the vessel wall, . . .", whereas in our current study, noncalcified plaque had to be at least 1 mm^2 in size. Thus, the prevalence of noncalcified plaque in Post et al.

(60%) was much higher than that in this study (only 20%). The CAD risk factor profile of the participants in these 2 studies also differed. For example, the mean age of participants in Post et al. was 53.2 (±6.5) years for HIV infected and 55.8 (±7.4) years for HIV-uninfected, compared to a mean age of our study participants of 45.6 (±7.9) years for HIV infected and 44.2 (±6.9) years for HIV uninfected. Consistent with their older age, study participants in Post et al. also had much more adverse CAD risk profiles than did ours. These differences may also explain why coronary plaque, especially noncalcified plaque, was more prevalent in the Post et al. study.

In contrast, both studies found that HIV infection was not significantly associated with the presence of calcified plaque. In Post et al., the unadjusted PR for calcified plaque by HIV infection was 0.88 (95% CI, 0.73, 1.06; P=0.19; based on the data in Table 2[14]), and adjusted PR was 1.05 (95% CI, 0.88, 1.27; P=0.58). In this study (men only), the unadjusted PR for calcified plaque stenosis by HIV infection was 1.08 (95% CI, 0.83, 1.41; P=0.55), and the adjusted PR was 1.02 (95% CI, 0.76, 1.37; P=0.89). In the earlier study by Lai et al.,[12] a significant association was found between cocaine and CAC, the magnitude of which was similar to that of our current study. However, unlike our current study, there was also an independent association found between HIV infection and CAC in AAs. Associations with coronary plaque and stenosis were not assessed in our earlier study. We cannot account for the difference in results regarding HIV infection and CAC prevalence between our earlier and our current study. The demographics of the sample were similar as was the CAD risk profiles and prevalence of CAC. Nonetheless, in our current study, with a sample size over 5 times larger than that in our earlier study, we have found that the associations between HIV infection and subclinical coronary atherosclerosis may be attributed to a markedly worse cardiovascular risk profile in the HIV infected compared to the HIV uninfected. Thus, after controlling for confounding factors, especially propensity score, some significant associations identified in the univariate analyses diminished.

It is critically important to emphasize that despite the fact that an overall nonsignificant association between HIV infection and subclinical coronary atherosclerosis was observed, the findings of this study should not be interpreted as evidence against existence of the adverse cardiovascular consequences of HIV infection. More-detailed analyses revealed that duration of ART use in HIV infected modified the overall association between HIV infection and subclinical coronary atherosclerosis—compared to those without HIV infection, those who were HIV infected and ART naïve were at significantly lower risk for the presence of any coronary stenosis, noncalcified plaque, and subclinical CAD (Table 3, I. comparing those HIV infected ART naïve with HIV uninfected); however, those who were HIV infected and had used ART ≥36 months were at significantly higher risk for the presence of any coronary stenosis (Table 3, III. comparing those HIV infected and ART use ≥36 months with HIV uninfected). These results may partly explain why no significant overall association was found between HIV infection and the presence of subclinical coronary atherosclerosis. The diametrically opposite effects of HIV infection for those who were ART naïve and those who had used ART for ≥36 months cancelled one another out, yielding an overall nonsignificant association between subclinical coronary atherosclerosis and HIV infection in the study population.

In previous literature, the associations between HIV infection and subclinical coronary atherosclerosis was rarely analyzed by duration of ART use. Thus, the associations derived from those studies may not be associations between HIV infection itself and subclinical coronary atherosclerosis. Further studies, especially longitudinal studies, are required to corroborate our results and investigate whether and why those who were HIV infected but ART naïve may have a lower risk of subclinical coronary atherosclerosis than HIV uninfected.

Notably, most of the ART use in our cohort was protease inhibitor (PI)-based, with little non-nucleoside reverse transcriptase inhibitor person time (Table 1) and not use of the newer integrase inhibitors. The D:A:D study also found an association between duration of PI use and clinical MI.[2] Incidence of MI increased from 1.53 per 1000 person-years in patients not exposed to PIs to 6.01 per 1000 person-years among patients exposed to PIs for >6 years. In another study, the relative hazard of MI was 0.8 (95% CI, 0.5–1.3) for men exposed to PI for <18 months, 1.5 (95% CI, 0.8–2.5) for men exposed for 18 to 29 months, and 2.9 (95% CI, 1.5–5.0) for men exposed for ≥30 months.[3] Our results may be demonstrating the role of ART, and specifically PIs, in promoting subclinical coronary atherosclerosis. There is some evidence suggesting that ART may improve endothelial dysfunction in a short term; however, long-term exposure to ART may worsen endothelial dysfunction.[22–24] Further studies are also needed to confirm these results.

Our study showed that cocaine use was independently associated with subclinical coronary atherosclerosis. This finding is consistent with other published data.[9,12,13] In our study, those who were HIV infected and ART naïve had a higher traditional cardiovascular risk than those without HIV infection, those without HIV infection had used cocaine significantly more commonly and had used cocaine significantly longer than those who were HIV infected and ART naïve (Table 7). Notably, the adverse effects association of long-term ART use with subclinical atherosclerosis was only found in cocaine users, but not in those who never used cocaine. The effect of cocaine use on subclinical atherosclerosis might

be stronger than traditional cardiovascular risk. This finding highlights the importance of reducing cocaine use in HIV-infected persons, especially in those who are on ART. Because ART is a lifelong treatment that improves survival in those with HIV infection, our finding suggests that reduced cocaine use must be one of highest priorities in fight against HIV/ART-associated comorbidities.

Our study also demonstrated that the adverse effects of long-term ART use may be modified by cocaine use. The results in Table 6 show that long-term use of ART may not impose significant risk of subclinical coronary atherosclerosis in those who never used cocaine, whereas the adverse effect of long-term ART use on subclinical coronary atherosclerosis is very apparent in chronic cocaine users. These findings strongly suggest that it is critically important to treat cocaine addiction in HIV-infected cocaine users because long-term ART use may be necessary to control HIV disease. Our data suggest that cocaine use is not only a risk factor for HIV transmission, but also a risk factor for subclinical atherosclerosis in HIV-infected persons, especially in those with long-term exposure to ART. Thus, treating cocaine addiction must be a high priority for managing HIV disease and preventing HIV/ART-associated subclinical and clinical CAD in HIV-infected AAs. Unfortunately, there are no US Food and Drug Administration–approved medications to treat cocaine addiction. Some studies suggest that transcranial magnetic stimulation of the dorsolateral prefrontal cortex or even cash-based incentive intervention may reduce cocaine use.[25,26] Further studies are needed to confirm these findings.

Our study has several strengths that should be mentioned: (1) Our study was performed in 1 medical center and 1 ethnic group. Thus, the effects of race or study site could not confound the findings of this study; (2) by employing the propensity score approach, the findings from this study should be more robust to potential hidden bias from unobserved confounding factors; and (3) our study only included participants without clinical CAD.

Nevertheless, our study also has several important limitations: (1) This investigation is a cross-sectional study, and although we explored whether HIV was associated with the presence of subclinical coronary atherosclerosis, in essence we had no knowledge as to whether or not subclinical coronary atherosclerosis was present before the HIV infection; (2) our study was conducted in an inner-city AA population. Approximately 75% of the study participants were cocaine users, and nearly all used alcohol. However, the prevalences of more-traditional risk factors were still considerably low. The results therefore may not be generalizable to other populations without exercising caution; (3) this study did not collect diet data on all study participants; (4) our study did not take into account the effects of other viral infections on subclinical coronary atherosclerosis; (5) this study could not include those with chronic kidney failure. Thus, the results may not be generalized without caution; (6) given that those who were on ART longer may have also had HIV-infection longer, because in a cross-sectional study it is impossible to separate the adverse effect of HIV infection from the effect of ART. For example, whereas DAD data suggest that ART plays a role, the SMART study clearly shows that HIV plays a larger role. Thus, to some extent, ART duration may be more a marker for HIV duration than for ART itself. Longitudinal studies are needed to address these important issues; and (7) based on our definition of never using cocaine, cocaine never users may have included "remote users," who had used cocaine 5 years before the enrollment of this investigation. However, this exposure misclassification error should be minimal given that (1) according to our longitudinal observations, few chronic cocaine users quit, and (2) this exposure misclassification error should be nondeferential.

Conclusions

These limitations notwithstanding, our findings may have important implications for the prevention of HIV/ART-associated CAD, especially in AAs. This study revealed a high prevalence of subclinical coronary atherosclerosis in AAs without cardiovascular symptoms, that CAD risk profiles are more adverse in AAs with HIV infection than in HIV uninfected, that long-term exposure to ART may increase the risk for subclinical coronary atherosclerosis, especially in chronic cocaine users, and that HIV infection per se may have no appreciable impact on subclinical coronary atherosclerosis in this population. Although our findings should be regarded as tentative and replication in other cohorts is needed, they suggest that it will be particularly important to prevent and retard coronary atherosclerosis, to aggressively manage traditional risk factors for coronary atherosclerosis in HIV-infected patients who will be receiving potentially long durations of ART, and that abstinence from cocaine or reduced cocaine use in HIV-infected individuals must be one of the highest priorities for preventing HIV/ART-associated coronary atherosclerosis.

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Disclosures

None.

References

1. Eugenin EA, Morgello S, Klotman ME, Mosoian A, Lento PA, Berman JW, Schecter AD. Human immunodeficiency virus (HIV) infects human arterial smooth muscle cells in vivo and in vitro: implications for the pathogenesis of HIV-mediated vascular disease. *Am J Pathol*. 2008;172:1100–1111.
2. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte Ad, El-Sadr W, Thiébaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723–1735.
3. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D; Clinical Epidemiology Group from the French Hospital Database. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS*. 2003;17:2479–2486.
4. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fätkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Markowitz N, Neuhaus J, Phillips A, Rappoport C. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355:2283–2296.
5. Margolis JR, Kannel WS, Feinleib M, Dawber TR, McNamara PM. Clinical features of unrecognized myocardial infarction–silent and symptomatic. Eighteen year follow-up: the Framingham study. *Am J Cardiol*. 1973;32:1–7.
6. Lai S, Bartlett J, Lai H, Moore R, Cofrancesco J Jr, Pannu H, Tong W, Meng W, Sun H, Fishman EK. Long-term combination antiretroviral therapy is associated with the risk of coronary plaques in African Americans with HIV infection. *AIDS Patient Care STDS*. 2009;23:815–824.
7. Meng Q, Lima JAC, Lai H, Vlahov D, Celentano DD, Strathdee SA, Nelson KE, Wu KC, Chen S, Tong W, Lai S. Coronary artery calcification, atherogenic lipid changes and increased erythrocyte volume in HIV-1 infected participants treated with protease inhibitors. *Am Heart J*. 2002;144:642–648.
8. Meng Q, Lima JAC, Lai H, Vlahov D, Celentano DD, Strathdee S, Nelson KE, Tong W, Lai S. Use of HIV protease inhibitors is associated with left ventricular morphologic changes and diastolic dysfunction. *J Acquir Immune Defic Syndr*. 2002;30:306–310.
9. Lai S, Lai H, Meng Q, Tong W, Vlahov D, Celentano D, Strathdee S, Nelson K, Fishman EK, Lima JAC. Effect of cocaine use on coronary calcification among black adults in Baltimore. *Am J Cardiol*. 2002;90:326–328.
10. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, Nasir K, Grinspoon SK. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2010;24:243–253.
11. Lai S, Lai H, Celentano DD, Vlahov D, Ren S, Margolick J, Lima JAC, Bartlett JG. Factors associated with accelerated atherosclerosis in HIV-1–infected persons treated with protease inhibitors. *AIDS Patient Care STDS*. 2003;17:211–219.
12. Lai S, Lima JAC, Lai H, Vlahov D, Celentano D, Tong W, Bartlett JG, Margolick JH, Fishman EK. HIV-1 infection, cocaine, and coronary calcification. *Arch Intern Med*. 2005;165:690–695.
13. Lai S, Fishman EK, Lai H, Moore R, Cofrancesco J, Pannu H, Tong W, Du J, Bartlett J. Long-term cocaine use and antiretroviral therapy are associated with silent coronary artery disease in cardiovascularly asymptomatic African Americans with HIV infection. *Clin Infect Dis*. 2008;46:600–610.
14. Post WS, Budoff M, Kingsley L, Palella FJ Jr, Witt MD, Li X, George RT, Brown TT, Jacobson LP. Associations between HIV infection and subclinical coronary atherosclerosis. *Ann Intern Med*. 2014;160:458–467.
15. Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, Schouten JT, Smieja M; Working Group 2. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. *Circulation*. 2008;118:e29–e35.
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. Erratum in: Ann Intern Med. 2011;155:408.
17. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol*. 2003;3:21.
18. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2935–2959.
19. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265–2281.
20. Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, Mogun H, Levin R, Kowal M, Setoguchi S, Hernández-Díaz S. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med*. 2014;370:2397–2407.
21. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. *Ann Intern Med*. 2002;137:693–695.
22. Dubé MP, Lipshultz SE, Fichtenbaum CJ, Greenberg R, Schecter AD, Fisher SD; Working Group 3. Effects of HIV infection and antiretroviral therapy on the heart and vasculature. *Circulation*. 2008;118:e36–e40.
23. Wolf K, Tsakiris DA, Weber R, Erb P, Battegay M; Swiss HIV Cohort Study. Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1. *J Infect Dis*. 2002;185:456–462.
24. Torriani FJ, Komarow L, Cotter BR, Murphy PM, Fichtenbaum CJ, Currier JS, Dubé MP, Squires KE, Gershenson M, Mitchell CK, Stein JH. Control of HIV infection is associated with rapid improvement in endothelial function sustained over 24 weeks: A5152s, a substudy of A5142. *Antivir Ther*. 2007;12(suppl 2):L15. Abstract.
25. Terraneo A, Leggio L, Saladini M, Ermani M, Bonci A, Gallimberti L. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: a pilot study. *Eur Neuropsychopharmacol*. 2016;26:37–44.
26. Lai H, Stitzer M, Treisman G, Moore R, Brinker J, Gerstenblith G, Kickler TS, Li J, Chen S, Fishman E, Lai S. Cocaine abstinence and reduced use associated with lowered marker of endothelial dysfunction in African Americans: a preliminary study. *J Addict Med*. 2015;9:331–339.