## Title

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# Incidence and progression of coronary artery calcium (CAC) in HIV-infected and HIV-uninfected men

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## Abstract

**Objective—**To determine whether HIV-infected men have either higher incidence or more rapid progression of coronary artery calcium (CAC) compared to HIV-uninfected controls.

**Design—**Prospective observational study.

**Setting—**Multicenter study in four USA academic research centers; University of Pittsburgh, Johns Hopkins University, University of California Los Angeles and Northwestern University.

**Participants—**825 men (541 HIV-infected and 284 HIV-uninfected) enrolled in the cardiovascular sub-study of the Multicenter AIDS Cohort Study who underwent serial cardiac CT imaging during a mean follow-up of 5 years (range, 2–8 years).

**Main Outcome Measures—**Incidence and progression of CAC assessed by cardiac computed tomography (CT).

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Matthew Budoff- cardiac CT scans, interpretation of results, funding, administrative support, manuscript writing
Mallory Witt- interpretation of results, administrative support, manuscript writing
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Wendy Post- interpretation of results, funding, administrative support, manuscript writing

**Results—**During follow-up, 21% of HIV-infected men developed incident CAC as compared to 16% of HIV-uninfected men. This association persisted after adjustment for traditional and HIV-associated risk factors: HR 1.64 [1.13–3.14]. However, there was no association between HIV serostatus and CAC progression among men with CAC present at baseline. Current smoking and increased insulin resistance, both modifiable risk factors, were independently associated with increased incidence of CAC. No evidence supporting an elevated risk for either CAC progression or incidence was found for either dyslipidemia or long-term usage of antiretroviral therapy.

**Conclusions—**In this large study of HIV-infected and HIV-uninfected men who underwent serial cardiac CT scan imaging, HIV-infected men were at significantly higher risk for development of CAC: HR 1.64 [1.13–3.14]. In addition, two important and modifiable risk factors were identified for increased incidence of CAC. Taken together these findings underscore the potential importance for smoking cessation and interventions to improve insulin resistance among HIV-infected men.

### Keywords

HIV; antiretroviral therapy; atherosclerosis; coronary artery calcium

## Introduction

The extended survival of HIV-infected people achieved through routine use of combination antiretroviral therapy (cART) has been accompanied by concerns regarding the long-term potential metabolic consequences of life-long antiretroviral therapy which are potentially atherogenic, e.g dyslipidemia, increased insulin resistance, and hyperglycemia. [1,2,3]. These data, as well as information from several observational studies suggest that chronic HIV infection itself is associated with an increased risk for major cardiovascular disease (CVD) events. This important avenue of research has focused attention on the potential role of HIV infection and its treatments in the pathogenesis of coronary artery disease and sudden cardiac death (SCD) among treated HIV-infected persons, although specific mechanisms leading to these increased risks are not well described [4,5,6,7]. Because coronary artery calcium (CAC) measurements have repeatedly been shown to be highly predictive of future coronary events in the general population [8,9,10,11], we and others have used computed tomography (CT) to study associations between CAC and traditional risk factors for subclinical atherosclerosis in HIV-infected populations.

This report presents data on both the incidence and progression of CAC among 825 men (541 HIV-infected and 284 HIV-uninfected) who participated in the Multicenter AIDS Cohort Study and underwent 2 or more cardiac CT scans over a mean follow-up of 5 years. Our major study objective was to investigate the important questions of whether HIV-infected compared to HIV-uninfected men are at greater risk for either incidence or progression of CAC after controlling for HIV-associated risk factors, especially duration of antiretroviral therapy as well as traditional CVD risk factors. We further sought to elucidate risk factors for incident CAC and CAC progression.

## Methods

### Study population

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective observational study that enrolled men who had sex with men (MSM) in four major United States cities: Baltimore, MD/Washington, DC, Chicago, IL, Los Angeles, CA, and Pittsburgh, PA. Active MACS participants over 40 years of age, without a history of prior coronary or cerebrovascular disease and who weighed less than 300 pounds were invited to undergo non-contrast CT scanning beginning in 2004 during the initial MACS CVD study (CVD1). Baseline CT scanning was completed in 945 men and 794 had a second CT scan a median 2.9 years later. The second MACS CVD study (CVD2) was initiated in 2010 and included both coronary CT angiography and non-contrast CAC scans. Analysis was restricted to men with at least two CAC scans (N=830), spanning up to 8.4 years follow-up. Men were also excluded from the study sample if they seroconverted during follow-up (N=5), yielding an analytic sample of 825. Men excluded from the analytic sample, mostly due to not having undergone a follow-up CT scan, were more likely to have hypertension (49% vs. 40%, p=0.05), but did not differ on other demographic or disease covariates, including use of antihypertensive medications or in presence or extent of CAC at baseline (data not shown). All participants gave informed consent to participate. The Institutional Review Board of each institution approved all studies.

### Computed tomography imaging

Non-contrast cardiac CT studies were performed in the initial MACS CVD1 study as described [12] and the MACS CVD2 study using multi-detector row CT scanners (64-MDCT at 3 sites and 320 MDCT at one site) at each site as previously described [13]. All cardiac CT scans included a minimum of 40 slices, spaced 2.5–3.0 mm apart, starting from 1 cm below the carina. CAC scores were computed using the Agatston method [14]. Although the CT technology evolved from electron beam CT scanners (EBT) used by 3 MACS centers in CVD1 to 64 and 320-MDCT imaging used in CVD2, the correlation between EBT and 64-MDCT has been shown to be exceptional, R=0.98 [15]. Presence of CAC was defined as an Agatston score >10.

### Exposure and covariates

At each study visit, HIV serostatus was determined using serologic testing (ELISA). Total cholesterol (TC) and HDL-C were measured from fasting and non-fasting blood samples. LDL-C was calculated from fasting blood draw samples with triglycerides < 400 mg/dL using the Friedewald equation. LDL-C was directly measured on fasting blood draw samples with triglycerides ≥ 400 mg/dL and on non-fasting blood draw samples. Lipid testing was performed at the Heinz Nutrition Laboratory at the University of Pittsburgh. Additional laboratory assays performed at the Heinz Lab included fasting blood glucose (FBG) and insulin, which were used to calculate the homeostatic model assessment of insulin resistance (HOMA-IR).

Demographic information was collected during the initial visit of the MACS CVD study, including age (years) and study site. Self-reported information on tobacco smoking status

(never/former/current) was collected at each study visit. Body mass index (BMI, kg/m$^2$) was calculated from weight and height measured at MACS semiannual study visits. Hypertension was defined as systolic blood pressure (mmHg) > 140 mm Hg or use of antihypertensive medication. Diabetes was defined as fasting glucose > 126 mg/dl or use of medication for diabetes.

## Statistical analyses

Baseline covariate distributions were compared between HIV-infected (HIV+) and HIV-uninfected (HIV−) participants using the Pearson chi-square test for categorical values and the Student's t-test of equal means or Wilcoxon rank sum test of equal medians for continuous variables. Cox proportional hazards models were used to model the multivariable-adjusted hazard ratios and 95% confidence intervals of incident CAC (Agatston score >10) by HIV serostatus among participants with no CAC at baseline. Proportionality assumptions were verified. Among participants with CAC present at baseline, linear random effects models with a random intercept and a random time slope were used to test whether rates of CAC progression over time differed by HIV serostatus. An interaction term between HIV serostatus and time was included in the models in order to estimate the effect of HIV serostatus on CAC progression with advancing age. The random effects for intercept and time slope were allowed to be correlated, and the covariance matrix for the random effects was conservatively assumed to be unstructured. Because of non-linearity between Agatston score and age, Agatston score was converted to the natural log.

For both the CAC incidence and CAC progression analyses, age was modeled as the time scale. Use of age as the study time scale both adjusts for age (potentially one of the strongest confounders between HIV infection and CAC incidence/progression over time) and allows for description of the association between HIV infection and CAC using a more clinically meaningful time scale than "time on study" would permit. The mean age at baseline was 51 (+/−SD 7) years and the mean age at the final visit was 55 (+/− SD 6) years. In order to utilize as much data as possible while remaining within the range of the majority of the data, the age for analysis was restricted to 42–70 years. For the analysis of incident CAC, the origin was therefore defined as age 42. For the CAC progression analysis, age was centered at 50, so that the interpretation of the model constant is therefore the average estimated natural log of the Agatston score at age 50. Age was also scaled to 5 years; the interpretation of the rate of change is therefore the averaged estimated change in the natural log of the Agatston score for every 5-year increase in age.

Missing covariate data was imputed using multiple imputation with chained equations. Baseline covariates with missing values and the numbers of missing values imputed include: smoking status (n=5), BMI (n=16), systolic blood pressure (n=2), hypertension medication use (n=4), diabetes medication use (n=6), fasting glucose (n=36), total cholesterol (n=7), HDL cholesterol (N-7), LDL cholesterol (n=9), triglycerides (n=38) and use of cholesterol-lowering medications (n=9).

Decisions regarding selection of confounding variables to be included in the model were made a priori based on knowledge regarding the variables and their association with HIV infection and CAC. A three-step model building process was used to adjust for confounders.

Model 1 adjusted for demographic characteristics, including race, study site and cohort (recruited before 2001 vs. recruited after 2001). Model 2 adjusted for Model 1 covariates as well as cardiovascular disease risk factors measured at baseline, including smoking status (never/former/current), BMI ($kg/m^2$), systolic blood pressure (mmHg), antihypertensive medication use, diabetes medication use, fasting glucose (mg/dL, log-transformed to account for non-linearity), total cholesterol (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), triglycerides (mg/dL, log-transformed to account for non-linearity), and use of cholesterol-lowering medication. In recognition of the time-varying nature of many of the covariates included in Model 2, Model 3 adjusted for Model 1 covariates and the average value of time-varying covariates (those covariates included in Model 2) over follow-up.

All analyses were performed in Stata Statistical Software, Release 13.0 (StataCorp, College Station, TX).

## Results

Baseline characteristics of the study population (Table 1) reflect similarities in the population that was the basis of our original report (13); all men included in the current study were seen at baseline in the first MACS cardiovascular study. Compared to HIV− men, HIV+ men were younger, more likely to be African-American, had lower BMI with less hypertension, had greater smoking exposure and were more likely to have lower HDL-cholesterol and greater usage of lipid lowering therapies. Overall, 67% of men studied were HIV-infected.

The unadjusted prevalence of CAC was similar by HIV serostatus, although CAC amount was lower among the HIV-infected men, consistent with our earlier findings. Of the 825 men with repeat cardiac CT scans available to evaluate CAC incidence, 124 (22.2%) whose baseline CAC score was <10 at the time of the first scan had CAC scores of >10 on the 2nd scan, CAC amounts were stable at low levels (<10 at baseline and <10 at follow-up scanning) in 434 (52.6%) of men studied; 171 (20.7%) had CAC >10 at both baseline and follow-up scanning. Due to the measurement precision of cardiac CT, only 9 men (1.1%) had inconsistent measurements of CAC, either regressing from scores of >10 to <10 (1.0%) or moving from scores of >10 to <10 and back to >10 (0.4%).

CAC incidence for both HIV-infected and HIV-uninfected men is shown in Figure 1. During follow-up, a higher hazard rate for incident CAC was observed in HIV+ than HIV− men (21.0% vs 16.4%, respectively). Increased likelihood of CAC incidence was strongly associated with increasing age, i.e. older age groups of both HIV-infected and HIV-uninfected men had significantly higher incidence rates of CAC than younger age groups.

To address the question of whether traditional and HIV-associated risk factors affect CAC incidence, several multivariable models were constructed as shown in Table 2. The hazard ratio (HR) in Model 1 for CAC incidence among HIV+ compared to HIV− men was 1.74 [1.15–2.62] adjusted for race, study site and cohort period. As compared to white men, African-American men had a reduced hazard for incident CAC, 0.58 [0.35–0.96]. Very little attenuation of risk was noted as additional covariates were added; in Model 2 the HR for

CAC incidence among HIV+ compared to HIV− men was similar to Model 1, 1.76 [1.14–2.70], even after additional adjustment for smoking history, BMI, systolic blood pressure, use of antihypertensive medication, fasting glucose, total cholesterol, LDL-cholesterol, triglycerides, lipid-lowering medication usage and HOMA-IR. African-American men again had a reduced hazard for incident CAC and only current smoking status was significantly associated with increased incident CAC in this participant group, HR 1.73 [1.04–2.87). In Model 3 the HR for CAC incidence among HIV+ compared to HIV− men was 1.64 [1.07–2.53]; this model included adjustment for the average value of covariates over the entire duration of follow-up. In model 3, African-American men again had reduced incidence of CAC compared to white men and current smoking was associated with increased CAC incidence, HR 1.89 [1.13–3.14]. Thus, even after adjustment for traditional and HIV-associated risk factors, a significant increased hazard remains for CAC incidence among HIV-infected MACS participants as well as a consistent increased risk of CAC incidence due to current smoking.

To evaluate risk factors for incident CAC among HIV-infected men, separate models were constructed including only these men (n=375); in this group, African-Americans again showed reduced hazard for incident CAC, 0.45 [0.25–0.83]. Factors associated with an increased hazard of incident CAC included current smoking, 2.26 [1.25–4.10] and increased HOMA-IR (log-transformed), 1.67 [1.05–2.65] (data not shown). No associations were observed for dyslipidemia, duration of HAART usage, HIV RNA level or CD4 cell count/$mm^3$ nadir and incident CAC. Importantly, this model uses covariates averaged over the follow-up period.

Progression of CAC occurred in the great majority of men among whom CAC was present at baseline. Among 267 men with CAC >10 at baseline, higher CAC Agatston scores were observed during follow-up in 258/267 (97%) with no difference observed by HIV serostatus in the proportion of men with CAC progression (96% of HIV+ and 97% of HIV− men). Displayed in Figure 2 are the unadjusted observed trajectories of CAC scores among HIV+ and HIV-men who had CAC > 10 at baseline. Overall, rates of progression were not significantly different by HIV serostatus, however these data reflect the natural history of coronary artery calcification as the amount of CAC roughly doubles every 3–5 years. Among both HIV-infected and HIV-uninfected men, CAC increased similarly from about 50 to 400–500 Agatston units in men ages 45 and 65.

To further evaluate whether there were differential progression rates of CAC by HIV serostatus, we analyzed 5-year rates of change in Agatston scores. Consistent with our multivariate models for incident CAC, very little attenuation of risk for both HIV-infected and HIV-uninfected men was observed as additional covariates were added in Models 2 and 3; as demonstrated by 5-year rates of change in CAC, no significant differences in CAC progression by HIV serostatus were thus observed (Table 3).

## Discussion

This report provides strong evidence that HIV-infected men were at substantially increased risk for incident CAC compared to HIV-uninfected men after controlling for both traditional

cardiovascular disease risk factors and HIV-associated risks, including cART duration. Among the HIV+ men, it is of note that current smoking and increased insulin resistance, both modifiable risk factors, were found to be independently associated with increased incidence of CAC. However, in this large group of very well-characterized HIV+ and HIV− men in the MACS, we found no differential rate of CAC progression by HIV serostatus, as evidenced by an overall 5-year rate of change in CAC score that was very similar in these two participant groups.

To our knowledge this is the largest study of HIV-infected men who underwent serial cardiac CT scan imaging with a similarly evaluated and appropriate HIV-uninfected comparison group. Taken together these findings underscore the potential importance for smoking cessation and interventions to improve insulin resistance among HIV-infected men.

Our report differs significantly from other previous studies that evaluated smaller numbers of individuals in that we did not ascertain an association between CAC progression and HIV infection. Guaraldi et al reported a limited sample of only 25 HIV-infected subjects and 13 HIV-uninfected controls and found an elevated rate of CAC progression among HIV-infected men, albeit over a much shorter (11 month median) follow-up period. This report also found that hypercholesterolemia was significantly associated with CAC progression, while our report did not confirm this finding. It is likely that such differences may be due to varying characteristics of the study populations as well as differential sample size [16]. Zona, et al reported on 240 HIV-infected subjects (68%male) who underwent repeat cardiac CT scans over a median 18.7 months. They concluded that increased age, higher BMI, follow-up time and epicardial adipose tissue (EAT) were all independent predictors of CAC progression; however, no HIV-uninfected controls were included in the study [17]. Similarly, Mangili, et al obtained serial cardiac CT scans on 255 HIV-infected patients (72% male) over a 3-year follow-up and report that coronary atherosclerosis progression is accelerated in HIV-infected persons; again, though, no age-appropriate HIV-uninfected persons were included as controls, a limitation regarding the central finding that CAC progression is accelerated among HIV-infected men [18].

Our study has important limitations. Perhaps most important is that it focuses exclusively on coronary artery calcium, and excludes measurement of non-calcified coronary plaque and stenosis, which have recently been shown in our cohort to be more prevalent among HIV-infected men [19]. These measures of coronary disease can be visualized only by using coronary CT angiography and may help explain the apparent disconnect between numerous earlier studies that showed little difference in either coronary calcium presence and extent by HIV serostatus in contrast to the several prior reports showing an association between HIV-infection and major cardiovascular events. It also is possible that the increased CAC incidence among HIV-infected men reported upon herein may, in part, be explained by an increased incidence of non-calcified plaque and subsequent transition to calcified plaque as measured in this report. Also, largely due to the early baseline evaluation of CAC that took place beginning in 2004 for our cohort, we do not have sufficient data regarding biomarkers of either systemic inflammation or elevated immune activation, both of which have been shown to be associated with coronary plaque [20]. We did not assess for measurement drift between CAC scans, however, the associations between HIV serostatus and incidence and

progression of CAC should not be influenced by drift, due to lack of differential misclassification. Last, we only included men since the MACS is a study of MSM, thereby precluding our ability to generate inferences about CAC incidence and progression in women or injection drug users.

This report will be followed by studies evaluating incidence and progression of non-calcified plaque and stenosis in the MACS, as our cardiovascular studies proceed. The MACS is currently repeating CTAs on the subgroup of men enrolled in the MACS cardiovascular study [19]. These studies will be critical to our understanding of the natural history of incidence, progression and risk factors for both non-calcified and calcified plaque in HIV-infected men.

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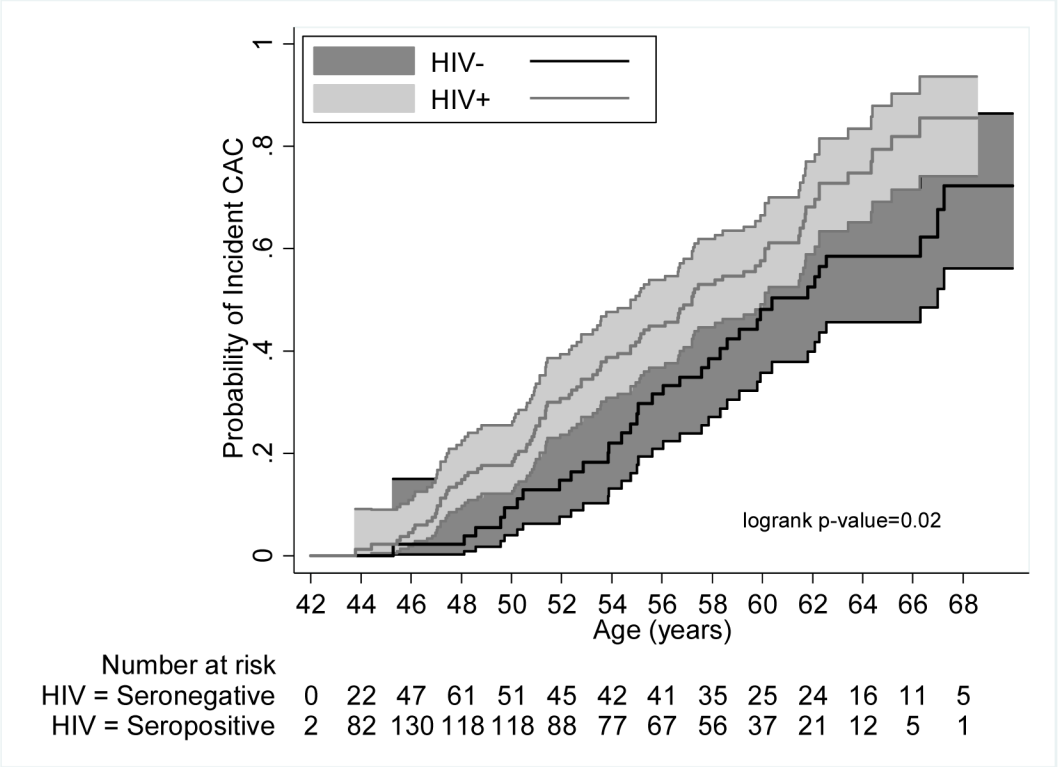


**Figure 1.**

Kaplan-Meier Estimate of the Cumulative Incidence of Coronary Artery Calcium[a] (CAC) by Baseline HIV Serostatus Among Participants with no Baseline CAC, N=558

a, CAC presence defined as Agatston score >10

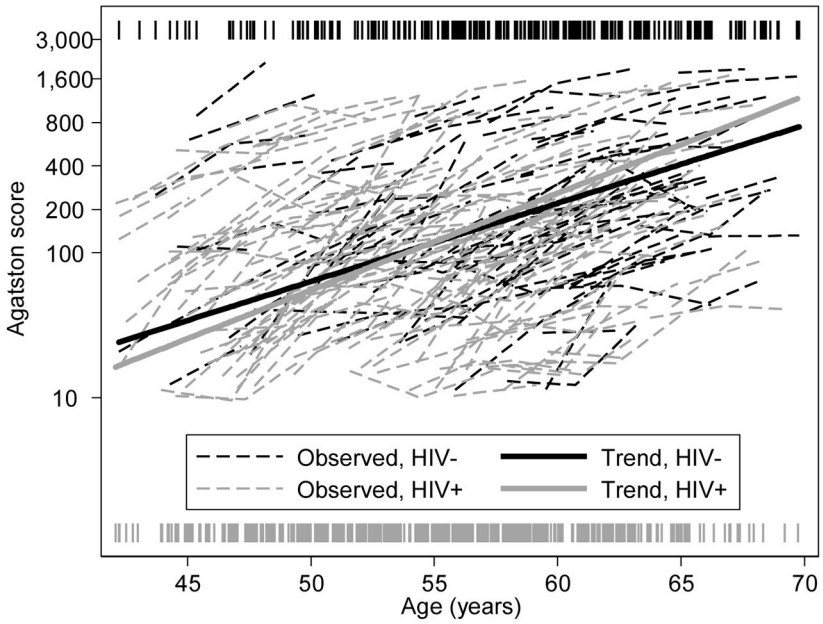


**Figure 2.**

Observed Trajectories of the Agatston[a] score by Baseline HIV Serostatus Among Participants with Baseline Coronary Artery Calcium[b] (CAC), with Marginal Trend, N=267

a, Agatston score graphed as the natural log. The x-axis presents the corresponding Agatston score for interpretability

b, CAC presence defined as Agatston score >10

Rug plots on top and bottom of the graph show the distribution of observed scores along the age range in HIV seropositive (bottom) and seronegative (top) men; there is one tick per observation).

## Table 1

Baseline Characteristics by HIV Serostatus, N=825

| Characteristic | Total Cohort (N=825) | HIV Seropositive (N=541) | HIV Seronegative (N=284) | P-value[a] |
|---|---|---|---|---|
| Age (years), mean (SD) | 50.5 (7.1) | 49.2 (6.3) | 53.0 (7.7) | <0.01 |
| Race, N(%) | | | | |
| Caucasian | 533 (64.6) | 332 (61.4) | 201 (70.8) | |
| African-American | 222 (26.9) | 160 (29.6) | 62 (21.8) | 0.03 |
| Hispanic and Other | 70 (8.5) | 49 (9.1) | 21 (7.4) | |
| Smoking status, N(%) | | | | |
| Never | 215 (26.1) | 133 (24.6) | 82 (28.9) | |
| Former | 353 (42.8) | 219 (40.5) | 134 (47.2) | 0.01 |
| Current | 252 (30.6) | 184 (34.0) | 68 (23.9) | |
| Body mass index (kg/m$^2$), mean (SD) | 25.9 (4.3) | 25.4 (4.1) | 26.8 (4.4) | <0.01 |
| Hypertension, N(%) | 315 (38.2) | 183 (33.8) | 132 (46.5) | <0.01 |
| Use of antihypertensive medication, N(%) | 186 (22.6) | 115 (21.3) | 71 (25.0) | 0.27 |
| Systolic blood pressure (mmHg), mean (SD) | 127.5 (14.1) | 126.0 (13.8) | 130.3 (14.2) | <0.01 |
| Diabetes, N (%) | 71 (8.6) | 49 (9.1) | 22 (7.8) | 0.82 |
| Diabetes medication use, N (%) | 46 (5.6) | 31 (5.7) | 15 (5.3) | 0.20 |
| Fasting glucose (mg/dL), mean (SD) | 102.1 (30.1) | 101.9 (28.2) | 102.4 (33.4) | 0.81 |
| HOMA-IR, mean (SD) | 4.56 (4.83) | 4.68 (4.85) | 4.35 (4.79) | 0.03 |
| Total cholesterol (mg/dL), mean (SD) | 196.8 (44.5) | 193.9 (46.8) | 202.3 (39.4) | 0.01 |
| HDL cholesterol (md/dL), mean (SD) | 46.6 (14.1) | 44.9 (14.5) | 49.9 (12.6) | <0.01 |
| Cholesterol lowering medication use, N (%) | 193 (23.4) | 140 (25.9) | 53 (18.7) | 0.02 |
| Agatston score >10, N (%) | 267 (32.4) | 165 (30.5) | 102 (35.9) | 0.11 |
| Agatston score, median (IQR) | 0 (0, 33.8) | 0 (0, 20.4) | 0 (0, 0) | 0.06 |
| **HIV Clinical Factors**[b] | | | | |
| Initiated HAART, N (%) | -- | 478 (88.4) | -- | -- |
| Duration of HAART use (years)[c], mean (SD) | -- | 6.6 (2.6) | -- | -- |
| CD4+ T-cell count (cell/mm$^3$), median (IQR) | -- | 519 (360, 704 | -- | -- |
| Nadir CD4+ T-cell count (cell/mm$^3$), median (IQR) | | 278 (156, 391) | -- | -- |
| Detectable HIV RNA (copies/mL), N (%) | -- | 210 (39.3) | -- | -- |
| HIV RNA (copies/mL)[d], median (IQR) | -- | 4703 (461, 27900) | -- | -- |
| History of AIDS-defining diagnosis, N (%) | -- | 70 (12.9) | -- | -- |

Abbreviations: dL, deciliters; IQR, interquartile range; kg, kilograms; m, meters; mg, milligrams; mm, millimeters; mmHg, millimeters of mercury; SD, standard deviation

[a] For continuous variables, P-value from Student's t-test or Wilcoxon ranksum test. P-values for categorical variables from chi2 test.

[b] Among participants with HIV only (N=541)

[c] Among HIV seropositive participants who have initiated HAART use (N=478)

[d] Distribution of viral load only among HIV seropositive participants with detectable HIV RNA (N=210)

**Table 2**

Hazard Ratios and 95% Confidence Intervals of the Association Between HIV Positive Serostatus at Baseline and Incident Coronary Artery Calcium[a] (CAC), N=558

| | MODEL 1 | | MODEL 2 | | MODEL 3 | |
|---|---|---|---|---|---|---|
| | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| HIV positive serostatus | 1.74 (1.15, 2.62) | 0.009 | 1.76 (1.14, 2.70) | 0.010 | 1.64 (1.07, 2.53) | 0.025 |
| Race | | | | | | |
| White | Referent | -- | Referent | -- | Referent | -- |
| Black | 0.58 (0.35, 0.96) | 0.035 | 0.51 (0.30, 0.87) | 0.013 | 0.50 (0.29, 0.85) | 0.011 |
| Hispanic | 1.51 (0.80, 1.82) | 0.201 | 1.48 (0.79, 2.78) | 0.224 | 1.35 (0.72, 2.53) | 0.351 |
| Post-2001 cohort (vs. pre-2001) | 1.51 (0.97, 2.33) | 0.071 | 1.39 (0.88, 2.22) | 0.161 | 1.45 (0.917, 2.30) | 0.116 |
| Smoking status | | | | | | |
| Never | -- | -- | Referent | -- | Referent | -- |
| Former | -- | -- | 1.14 (0.71, 1.85) | 0.581 | 1.16 (0.72, 1.88) | 0.540 |
| Current | -- | -- | 1.73 (1.04, 2.87) | 0.036 | 1.89 (1.13, 3.14) | 0.015 |
| Body mass index | -- | -- | 1.02 (0.97, 1.08) | 0.462 | 1.00 (0.95, 1.05) | 0.993 |
| Systolic blood pressure | -- | -- | 1.00 (0.99, 1.02) | 0.565 | 1.00 (0.99, 1.02) | 0.604 |
| No anti-hypertensive medication use | -- | -- | 1.05 (0.65, 1.69) | 0.855 | 0.80 (0.51, 1.23) | 0.308 |
| Ln (fasting glucose) | -- | -- | 0.67 (0.17, 2.63) | 0.569 | 0.58 (0.12, 2.91) | 0.510 |
| Diabetes medication use | -- | -- | 1.09 (0.45, 2.61) | 0.848 | 0.91 (0.40, 2.05) | 0.812 |
| Ln (HOMA-IR) | -- | -- | 1.29 (0.88, 1.91) | 0.437 | 1.36 (0.89, 2.06) | 0.149 |
| Total cholesterol | -- | -- | 1.00 (0.99, 1.01) | 0.437 | 1.00 (1.00, 1.01) | 0.164 |
| HDL cholesterol | -- | -- | 1.01 (1.00, 1.02) | 0.119 | 1.00 (0.99, 1.02) | 0.512 |
| Cholesterol lowering medication use | -- | -- | 1.11 (0.70, 1.77) | 0.646 | 1.10 (0.72, 1.68) | 0.650 |

[a] CAC presence defined as Agatston score >10

[b] Model 1 adjusted for race (White/Black/Hispanic or Other), study site, and cohort (pre- or post-2001)

[c] Model 2 adjusted for Model 1 covariates plus covariates measured at baseline: smoking status (never/former/current), BMI ($kg/m^2$), systolic blood pressure (mmHg), antihypertensive medication use, diabetes medication use, fasting glucose (mg/dL, log-transformed), HOMA-IR (mmol/L x uU/ml, log-transformed), total cholesterol (mg/dL), HDL cholesterol (mg/dL), and use of cholesterol-lowering medication

[d] Model 3 adjusted for Model 1 covariates plus average value of time-varying covariates over follow-up: smoking status (never/former/current), BMI ($kg/m^2$), systolic blood pressure (mmHg), antihypertensive medication use, diabetes medication use, fasting glucose (mg/ld., log-transformed), HOMA-IR (mmol/L x uU/ml, log-transformed), total cholesterol (mg/dL), HDL cholesterol (mg/dL), and use of cholesterol-lowering medication

## Table 3

Multivariable-adjusted Estimates[a] and Differences in Estimates of ln(Agaston Scores)[b] at Age 50 and in 5-year Rates of Change ln(Agatston Score)[b] by Baseline HIV Serostatus Among Participants with Baseline Coronary Artery Calcium[c] (CAC), N=267

| | ln(Agatston score) at Age 50 | | Rate of 5-year Change in ln(Agatston score) | |
|---|---|---|---|---|
| | **Estimate (95% CI)** | **P-value** | **Estimate (95% CI)** | **P-value** |
| Model 1[d] | | | | |
| HIV seropositive, N=165 | 3.97 (3.59, 4.35) | <0.001 | 0.72 (0.63, 0.82) | <0.001 |
| HIV negative, N=102 | 4.10 (3.67, 4.51) | <0.001 | 0.61 (0.49, 0.73) | <0.001 |
| Difference | −0.12 (−0.52, 0.27) | 0.536 | 0.12 (−0.04, 0.27) | 0.140 |
| Model 2[e] | | | | |
| HIV seropositive, N=165 | 3.54 (2.92, 4.15) | <0.001 | 0.73 (0.64, 0.82) | <0.001 |
| HIV negative, N=102 | 3.64 (3.01, 4.25) | <0.001 | 0.61 (0.49, 0.73) | <0.001 |
| Difference | −0.10 (−0.51, 0.31) | 0.635 | 0.12 (−0.03, 0.28) | 0.122 |
| Model 3[f] | | | | |
| HIV seropositive, N=165 | 3.59 (2.95, 4.22) | <0.001 | 0.73 (0.63, 0.82) | <0.001 |
| HIV negative, N=102 | 3.76 (3.15, 4.38) | <0.001 | 0.61 (0.49, 0.74) | <0.001 |
| Difference | −0.18 (−0.57, 0.22) | 0.388 | 0.11 (−0.04, 0.27) | 0.152 |

[a] Estimated from linear mixed models

[b] Agatston score modeled as the natural log to account for non-linearity.

[c] CAC presence defined as Agatston score >10

[d] Model 1 adjusted for race (White/Black/Hispanic or Other), study site, and cohort (pre- or post-2001)

[e] Model 2 adjusted for Model 1 covariates plus covariates measured at baseline: smoking status (never/former/current), BMI (kg/m$^2$), systolic blood pressure (mmHg), antihypertensive medication use, diabetes medication use, fasting glucose (mg/dL, log-transformed), HOMA-IR (mmol/L x uU/ml, log-transformed), total cholesterol (mg/dL), HDL cholesterol (mg/dL), and use of cholesterol-lowering medication

[f] Model 3 adjusted for Model 1 covariates plus average value of time-varying covariates over follow-up: smoking status (never/former/current), BMI (kg/m$^2$), systolic blood pressure (mmHg), antihypertensive medication use, diabetes medication use, fasting glucose (mg/dL, log-transformed), HOMA-IR (mmol/L x uU/ml, log-transformed), total cholesterol (mg/dL), HDL cholesterol (mg/dL), and use of cholesterol-lowering medication