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Comparison of Racial Differences in Plaque Composition and Stenosis among HIV Positive and Negative Men from the Multicenter Aids Cohort Study (MACS)

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Abstract

Previous studies demonstrated that blacks have less coronary artery calcification (CAC) than whites. We evaluated racial differences in plaque composition and stenosis in the Multicenter AIDS Cohort Study (MACS). HIV positive and negative men completed non-contrast cardiac CT if they were 40–70 years, weighed <300 pounds, and had no prior history of cardiac surgery or revascularization, and if eligible, coronary CT angiography (CTA). There were 1001 men who underwent CT scans and 759 men had CTA. We measured CAC on non-contrast CT, and total plaque, non-calcified, calcified, and mixed plaque, and identified coronary stenosis >50% on CTA. The association of presence and extent of plaque with race was determined after adjustment for HIV serostatus, cardiovascular risk factors and measures of socioeconomic status. The prevalences of any plaque on CTA and non-calcified plaque were not different between black and white men; however, black men had lower prevalences of CAC (Prevalence ratio (PR)=0.79, p=0.01), calcified plaque (PR=0.69, p=0.002), and stenosis >50% (PR=0.59, p=0.009). There were no associations between black race and extent of plaque in fully adjusted models. Using log-linear regression, black race was associated with a lower extent of any plaque on CTA in HIV positive men (estimate=−0.24, p=0.051) but not in HIV negative men (0.12, p=0.50, HIV interaction

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p=0.005). In conclusion, a lower prevalence of CAC in black compared to white men appears to reflect less calcification of plaque and stenosis rather than a lower overall prevalence of plaque.

Keywords

Epidemiology; plaque; coronary angiography; coronary artery disease; HIV

Introduction

It is well-established that there are racial differences in coronary artery calcification (CAC), a measure of subclinical atherosclerosis and potent predictor of future coronary events.[1–3] Despite greater coronary risk factors and cardiovascular morbidity found in blacks,[4,5] blacks have a paradoxically lower prevalence of CAC[6–8] and less obstructive coronary artery disease compared to whites.[9,10] It is not known whether the lower prevalence of CAC is secondary to a lower overall prevalence of atherosclerotic plaque or whether it is secondary to a lower proportion of calcified relative to non-calcified plaque for any given plaque volume. Moreover, it is unknown how the presence of HIV infection affects these racial differences. In the Multicenter AIDS Cohort Study (MACS), we previously described that HIV positive men have a higher prevalence and extent of non-calcified plaque than HIV negative men.[11] In this manuscript, we evaluated racial differences in CAC, plaque composition, and coronary artery stenosis. We also tested for interactions of HIV serostatus on racial differences in plaque and stenosis.

Methods

Established in 1984, the MACS cohort has enrolled men who have sex with men, both seropositive and negative, during three enrollment periods from 1984 to 2003 in Baltimore, Chicago, Pittsburgh and Los Angeles.[12] A cross-sectional cardiovascular study within the MACS enrolled participants from all sites who were 40–70 years, weight < 300 lbs, and without prior history of heart surgery or coronary angioplasty. The Institutional Review Boards of all participating sites approved the study.

Participants were seen as part of routine MACS research visits for standardized interviews, physical examination, and blood and urine laboratory collection every 6 months. Data were collected regarding CAD risk factors including age, blood pressure, diabetes and impaired fasting glucose, dyslipidemia, smoking, medication use, body mass index (BMI) and HIV clinical parameters. Hypertension was defined as systolic blood pressure (BP) >140 mm Hg, or diastolic BP > 90 mm Hg, or self-reported use of anti-hypertensive medication. Diabetes mellitus was defined as fasting serum glucose ≥ 126 mg/dL or use of medications to treat diabetes. Race/ethnicity was based on self-report.

All participants completed a non-contrast CT scan for CAC scoring while those with atrial fibrillation, chronic kidney disease (estimated glomerular filtration rate <60 ml/min/m^2 by the MDRD equation within 30 days), or a contrast allergy were excluded from CTA. Participant heart rates were optimized, and scanned with ECG triggered protocols as

previously described.[13] In those few men whose heart rate was too fast or irregular, retrospective gating was used.

Non-contrast CT scans were analyzed for CAC using the Agatston method.[14] CTA images were analyzed using the modified 15-segment model of the American Heart Association for plaque presence and extent, coronary artery stenosis, and plaque composition.[15] The total plaque score (TPS) was calculated by summing the plaque size score for all assessable coronary segments that demonstrated any plaque with a maximum score of 45. Calcified atherosclerotic plaque was defined as any structure with attenuation >130 HU visualized separately from the intravascular lumen, identified in at least two independent planes. Non-calcified atherosclerotic plaque was defined as any discernible structure that could be clearly assignable to the vessel wall, with a CT density less than the contrast-enhanced coronary lumen but greater than the surrounding connective tissue, and identified in at least two independent planes. Finally, mixed plaque included lesions with less than 50% of plaque area occupied by calcium. The noncalcified plaque score (NCPS), mixed plaque score (MPS) and calcified plaque score (CPS) were calculated by summing the plaque scores in each segment separately.

Separate Poisson regressions with robust variance[16] were used to evaluate associations between self-reported race/ethnicity and the presence of plaque or stenosis. Presence of plaque was defined as CAC Agatston score > 0 from non-contrast CT scans and as TPS, NCPS, CPS, and MPS greater than 0 on CTA. Coronary stenosis was defined as greater than 50% in any coronary segment. Initial models adjusted for age, HIV serostatus, CT scanning center, and cohort status (enrollment pre- or post-2001) and included race as a predictor variable with white as the reference group. Additional analyses were then performed with further adjustment for CAD risk factors and education (college versus no college), income, and employment as measures of socioeconomic status (SES). Among men with plaque, linear regression was used to assess the extent of plaque present for CAC, TPS, CPS, MPS, and NCPS in natural log scale using the same models described above. Analyses were performed in the combined cohort and a race*HIV interaction term was included in the model to test for differences in the associations between race and plaque between HIV positive and negative men. For missing CAD risk factors, multiple imputation was used. Missing values were imputed five times based on the distribution of covariates using a Markov chain Monte Carlo method assuming multivariate normality.[17] All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Figure 1 was created by using TIBCO Spotfire S+ 8.2 (TIBCO Software Inc. Palo Alto, CA). Statistical significance was established at a p-value less than 0.05.

Results

A total of 1001 non-contrast CT scan and 759 CTA results were available for analysis. Characteristics of the three ethnic groups are show in Table 1 with p-values reflecting differences when compared to white men. Although not included in the plaque analyses due to small sample size and heterogeneity within the group (Hispanics, Asians, etc.), Hispanic/Other was included in the table for complete cohort comparison. There were a total of 581 white men and 305 black men. Black men were younger and more likely to have diabetes,

use diabetes medications, to be current smokers and had more smoking pack-years compared to white men. There were no significant differences between black and white men with respect to hypertension, systolic blood pressure, use of hypertensive medications, or BMI. Total and LDL cholesterol and triglycerides were lower in black men, whereas HDL cholesterol was higher. Black men were less likely to be taking lipid-lowering medication, to have attended college, be employed, or have an income greater than $50,000 per year compared with white men. The prevalence and extent of plaque subtypes stratified by race/ethnicity are presented in Table 2.

After adjusting for age, HIV serostatus, study center, and cohort status (minimally adjusted model), black men had a lower prevalence of CAC (Table 3). These results did not change substantially when adjusted for CAD risk factors and measures of SES. Among men with CAC present, there was no association between race and extent of CAC. In minimally adjusted models, there was no significant difference in prevalence of any plaque between black and white men, which persisted after adjustment for CAD risk factors and measures of SES. In men with plaque present on CTA, there was a significant inverse association between the extent of any plaque (total plaque score) and black race, after minimal adjustment. However, after further adjustment for CAD risk factors and SES this association was no longer statistically significant. In addition, there were no differences between black and white men in the extent of any of the plaque subtypes seen on CTA, including non-calcified, calcified or mixed plaque.

When minimally adjusted, black men had a lower prevalence of calcified plaque. This remained statistically significant after adjustment for CAD risk factors and measures of SES. There was a lower prevalence of mixed plaque in black men after minimal adjustment, which became borderline significant after adjustment for CAD risk factors and measures of SES.

After minimal adjustment, there was no association between race and non-calcified plaque nor after adjustment for CAD risk factors and measures of SES. After adjustment for age, HIV serostatus, study center, and cohort status, black men had a lower prevalence of stenosis greater than 50%, which was not substantially changed after adjustment for CAD risk factors and measures of SES. Figure 1 shows the prevalence ratios with confidence intervals of each plaque type for black men compared to white men from the fully adjusted models.

We evaluated whether associations between black race and coronary atherosclerosis differed by HIV serostatus by including an HIV interaction term in the multivariate model (Table 4). There was a significant HIV interaction for race and extent of any plaque (TPS) on CTA in minimally adjusted model, which persisted after adjustment for CAD risk factors and measures of SES. Using linear regression, there was a borderline association between black race and less overall plaque in HIV positive men but not in HIV negative men. There was also a significant HIV interaction for race and presence of non-calcified plaque in the minimally adjusted models, which was borderline statistically significant after adjustment for CAD risk factors and measure of SES. There was a significant HIV interaction for race and extent of mixed plaque on CTA in the minimally adjusted model that did not persist

after adjustment for CAD risk factors and measures of SES. Although none of the other HIV interaction tests were statistically significant in the fully adjusted models, there were several borderline significant interactions.

Discussion

In this cohort, we found black men had a lower prevalence of CAC, calcified plaque on CTA, coronary stenosis greater than 50% and a trend towards a lower prevalence of mixed plaque when compared with white men. More importantly, the prevalence of any plaque and non-calcified plaque did not differ by race. Although a lower prevalence of CAC and coronary stenosis have been described in other studies, the novel use of coronary CTA in our study allows a more detailed and through assessment of plaque. Our findings suggest that a lower prevalence of CAC in black men appears to reflect less calcification of plaque rather than a lower overall prevalence of plaque. CAC is a marker of subclinical atherosclerosis and is known to be a very potent predictor of cardiovascular events in the general population.[1–3] Since calcified plaque reflects more advanced stable plaque, this risk is thought to be through its association with overall burden of atherosclerosis as seen on autopsy studies.[18,19] However, our findings suggest that the association between CAC and overall plaque may be different in black men.

The association we found between black race and a lower prevalence of CAC was similar to what was seen in the Multi-Ethnic Study of Atherosclerosis (MESA). When compared to whites, Hispanics, and Chinese, blacks had the lowest prevalence and extent of coronary calcification, which remained after adjusting for cardiovascular risk factors.[6] Similar racial differences for CAC prevalence were subsequently confirmed.[20] Our study adds to this knowledge by including CTA with further characterization of NCP and overall plaque burden.

In additional to a lower prevalence of calcified plaque, we also found that black men had a lower prevalence of coronary stenosis > 50% than white men. Similar results were seen in a previous study in symptomatic patients presenting with angina,[9] and in the CONFIRM registry.[10] However, these results appear contradictory to what is known about higher rates of cardiovascular mortality in the black population.[5] One potential mechanism for lower rates of cardiovascular mortality in white men is the presence of more calcified coronary plaque as compared to their black counterparts. This may be relevant given the evidence that non-calcified plaque may be more prone to rupture and is associated with increased risk for mortality.[21] Although black men had a lower prevalence of stenosis greater than 50%, it is known that roughly two thirds of myocardial infarctions occur at sites lacking high-grade stenosis with superimposed plaque rupture and thrombosis formation. These lesions may be less likely to be symptomatic or identified on conventional stress testing prior to plaque rupture.[22–24]

A smaller retrospective study compared black and demographic (age and sex) matched white patients undergoing CTA who presented with chest pain and an intermediate probability of CAD. After adjustment for CAD risk factors, they also found a lower prevalence of calcified plaque in black patients.[25] However, unlike our study, they found

that black patients had an increased prevalence and extent of non-calcified plaque. There were no significant ethnic differences in the prevalence or extent of overall plaque burden, stenosis greater than 50%, or mixed plaque. This study had several crucial differences compared to ours. The patients presented with angina and were deemed intermediate risk by Framingham score whereas our cohort is generally without known clinical CAD, there were no adjustments made for measures of socioeconomic status, and the sample size was much smaller and contained 33% men.

In patients with HIV, life expectancy continues to improve with highly active antiretroviral therapy (HAART) and nearly matches the general population when viral replication is well-controlled.[26] As individuals with HIV are living longer, fewer are dying from AIDS-related illnesses. Instead, age-related diseases, such as cardiovascular disease, are increasing in this population.[27] Furthermore, some studies show that individuals with HIV have more atherosclerosis and cardiovascular disease compared to HIV negative individuals.[11,28]

We tested for interactions between race and HIV, and found a significant interaction only for the extent of total plaque. However, even though the other interactions were not statistically significant, the significant associations between black race and plaque/stenosis were only seen in the HIV positive men, and not in the HIV negative men. This may be partially due to the lower power in the HIV negative group, due to the smaller sample size, as reflected by wider confidence intervals. Although not statistically significant among the HIV negative men, an inverse association between black race and calcified plaque and >50% stenosis was observed. However, the significant interaction with extent of total plaque and other borderline interactions suggest that HIV may influence some of the associations between race and coronary plaque morphology through unidentified mechanisms. We repeated the analyses in HIV positive men including adjustment for HIV specific factors, and the results were not substantially different.

This study has several strengths, including the ability to characterize racial differences in coronary plaque presence, extent, composition and stenosis using CTA, rather than non-contrast CT scans, which provide less detailed characterization of plaque. The sample size was large and included a well-characterized cohort, with HIV positive and negative men from a similar background. Also, our analyses included detailed adjustment for socioeconomic status, which is an important possible confounder when studying racial differences. Limitations of this study include the cross-sectional study design, the inclusion of men only, possible residual confounding, and the small sample size of other ethnicities. Although there are some differences in cardiovascular risk factors seen between our white and black cohorts, we controlled for these differences with multivariable regression analyses. Furthermore, despite higher prevalences of many cardiovascular risk factors that would likely increase atherosclerosis, black participants were still found to have less CAC, but similar overall plaque burden and non-calcified plaque. Further investigation into these identified racial differences in plaque composition and stenosis is needed to understand mechanisms for its development and potential implications for cardiovascular events and prevention in high-risk black men.

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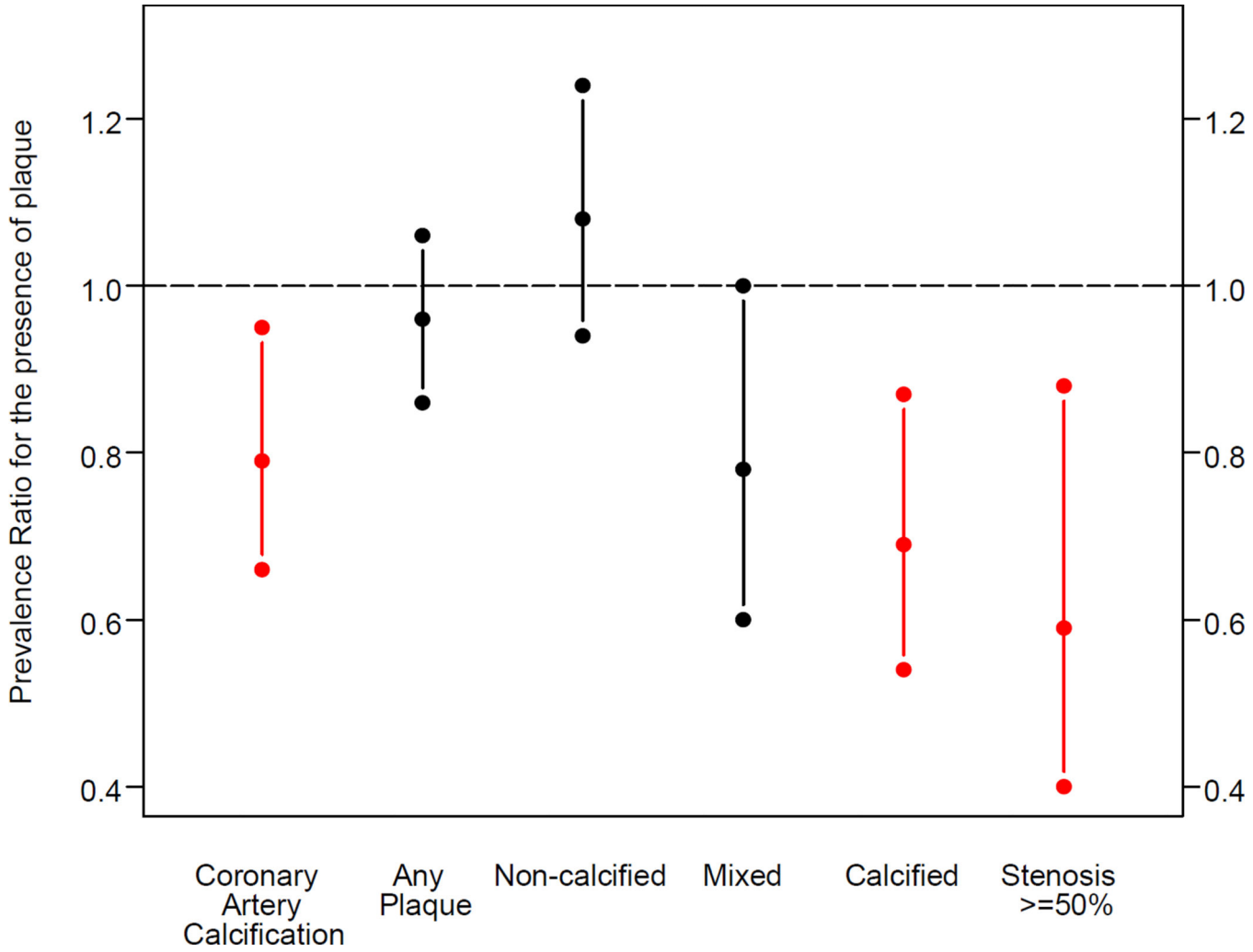

Figure 1.

Prevalence Ratios with 95% confidence intervals for comparing presnece of plaque and coronary stenosis greater than 50% for black men to white men after adjustment for age, HIV serostatus, study center, cohort status, measures of socioeconomic status, and CAD risk factors.

Table 1

Characteristics of Study Population

Variable	White	Black	P value*	Hispanic/other	P value †
	N=581	N=305		N=115	
Age (years)	56.7 (6.7)	51.6 (6.1)	<0.001	49.2 (5.7)	<0.001
Hypertension	48.1%	52.1%	0.27	38.1%	0.05
Systolic Blood Pressure (mm Hg)	128.1 (13.7)	127.7 (16.3)	0.62	121.4 (14.7)	<0.001
Hypertension medications	33.5%	36.4%	0.39	31.3%	0.65
Diabetes mellitus	9.2%	14.8%	0.01	13.8%	0.15
Diabetes medications	6.1%	10.6%	0.02	10.4%	0.09
Tobacco use					
Never smoked	29.7%	17.4%	<0.001	23.5%	0.09
Current smoker	17.1%	48.7%		25.2%	
Former smoker	53.2%	33.9%		51.3%	
Smoking pack-years**	1.3 (0–26.5)	8.6 (0.1–22)	0.002	1.2 (0–7.9)	0.11
Body Mass Index (kg/m^2)	26.4 (4.5)	26.9 (5.2)	0.54	26.5 (3.9)	0.73
Glucose (mg/dL)	100.1 (±19.9)	103.9 (±34.4)	0.89	105.2 (±41)	0.60
Total Cholesterol (mg/dL)	191.7 (±40.6)	182.5 (±36.8)	0.003	193.9 (±44.1)	0.68
LDL Cholesterol (mg/dL)	110.5 (±33.7)	101.7 (±33.4)	<0.001	112.3 (±37.6)	0.90
HDL Cholesterol (mg/dL)	49.2 (±15.3)	53.5 (±18.9)	0.002	48.5 (±13.4)	0.71
Triglycerides (mg/dL)	159.7 (±115.2)	140.4 (±113.9)	<0.001	174.4 (±115.9)	0.14
Lipid lowering meds	41.5%	17.2%	<0.001	28.7%	0.01
Education – College	64.2%	24.9%	<0.001	40.9%	<0.001
Income (<$20,000)	20.8%	64.9%		45.9%	
Income ($20,000–49,000)	25.5%	20.7%		21.6%	
Income (> $50,000)	53.7%	14.4%	<0.001	21.6%	<0.001
Employment	66.8%	37.8%	<0.001	63.5%	<0.001
HIV Seropositive	55.9%	68.9%	<0.001	72.2%	0.001
HIV Clinical Factors§	N=325	N=210		N=83	

Variable	White	Black	P value*	Hispanic/other	P value †
Undetectable Viral Load	90.3%	70.5%	<0.001	81.5%	0.03
HIV RNA (copies/mL)&	1440 (104–12200)	667 (194–34100)	0.49	239 (89–4920)	0.49
CD4+ T-cell count (cells/mm^3)	600 (436–770)	597 (405–773)	0.38	628 (477–757)	0.58
CD4+ T-cell nadir (cells/mm^3)	238 (144–329)	260 (127–335)	0.52	240 (129–323)	0.90
On HAART	97.5%	92.4%	0.005	98.8%	0.49
Protease inhibitor use	47.1%	48.6%	0.74	55.5%	0.18
Time on HAART (years)	13.4 (9.7–14.5)	10.1(7.1–13.2)	<0.001	12.3(9.4–12.6)	0.20
History of clinical AIDS	17.8%	10.5%	0.02	9.6%	0.07

Data are presented stratified by Race. Laboratory Glucose and Triglycerides results represent fasting levels. Data are reported as mean (standard deviation) or percentage. P values are unadjusted.

*P value comparing white participants to black participants.

†P value comparing white participants to Hispanic/other participants.

**Median (interquartile range: 25%– 75%) for non-normally distributed variables and mean (SD) for normally distributed variables.

§Among HIV positive men.

&Among 107 HIV positive men with detectable HIV RNA (>50 copies/mL) levels. HAART= highly active retroviral therapy. Values for the following number of men were missing and imputed for multiple regression analyses- hypertension medications (11), body mass index (27), diabetes medications (11), smoking pack-years (5), lipid medications (20), total and HDL cholesterol (28), systolic blood pressure (43), fasting glucose (36), income (34), employment (15).

Table 2

Computed Tomography Scan Results

CT Scan Parameters	White	Black	Hispanic/Other	Total
Non-Contrast CT Scans (N)	581	305	115	1001
Coronary artery calcium present	62.3%	40.7%	35.7%	52.6%
Coronary artery calcium score among those with calcium	82 (25–221)	49 (17–186)	41 (24–109)	71
Contrast-Enhanced CT Scans (N)	436	230	93	759
Prevalence of any coronary artery plaque	82.3%	70.4%	62.4%	76.3%
Prevalence of non-calcified plaque	61.5%	59.6%	47.3%	59.2%
Prevalence of mixed plaque	40.6%	23.9%	23.7%	33.5%
Prevalence of calcified plaque	45.0%	23.9%	29.0%	36.6%
Prevalence of any coronary artery stenosis > 50%	21.1%	8.7%	9.7%	12.9%
Total plaque score (TPS)	3 (1–7)	2 (0–4)	1 (0–4)	2 (1–5)
Non-calcified plaque score (NCPS)	1 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)
Mixed plaque score (MPS)	0 (0–2)	0 (0–0)	0 (0–0)	0 (0–1)
Calcified plaque score (CPS)	0 (0–2)	0 (0–0)	0 (0–1)	0 (0–1)

Plaque variables are reported as median and interquartile range (IQR) or percentage of men with plaque

Table 3

Associations between Race and Coronary Artery Plaque

Prevalence of plaque	**Minimally adjusted model**		**Adjusted for CAD risk factors and and socioeconomic status**	
Plaque Outcome	Prevalence ratio (95% CI)	P value	Prevalence ratio (95% CI)	P value
Non-Contrast CT Scans (N=1001)				
Coronary artery calcium	0.76 (0.64–0.90)	0.002	0.79 (0.66–0.95)	0.01
Contrast CT Scans (N=759)				
Any plaque	0.94 (0.84–1.05)	0.28	0.96 (0.86–1.06)	0.38
Non-calcified plaque	1.01 (0.87–1.17)*	0.91	1.08 (0.94–1.24)	0.25
Mixed plaque	0.74 (0.55–1.00)	0.047	0.78 (0.60–1.00)	0.054
Calcified plaque	0.63 (0.48–0.83)	0.001	0.69 (0.54–0.87)	0.002
Stenosis > 50%	0.48 (0.28–0.81)	0.006	0.59 (0.40–0.88)	0.009
Extent of Plaque **Plaque Outcome**	Mean Difference (95% CI)	P value	Mean Difference (95% CI)	P value
Non-Contrast CT				
Coronary artery calcium (N=527)	−0.20	0.36	−0.19	0.42
Contrast CT Scans				
Total plaque score (N=579)	−0.23*	0.01	−0.13*	0.17
Non-calcified plaque (N=449)	−0.12	0.14	−0.14	0.13
Mixed plaque (N=254)	−0.14*	0.32	0.02	0.90
Calcified plaque (N=278)	0.03	0.88	0.09	0.56

Minimally adjusted model includes age, HIV serostatus, study center, and cohort status. Model 2 includes the minimally adjusted model, CAD risk factors, and measures of socioeconomic status. CAD risk factors include antihypertensive medication use, systolic blood pressure among those not on antihypertensive medications, diabetes medication use, fasting glucose among those not on diabetes medications, use of lipid-lowering medications, total and HDL cholesterol among those not on lipid-lowering medications, body mass index and smoking (pack-years). Measures of socioeconomic status include education, income greater than $50,000 per year, and employment.

* HIV interaction P-value < 0.05.

Prevalence ratio = black men compared to white men. Scores less than 1 signify a lesser prevalence of plaque than white men. Scores greater than 1 signify a greater prevalence of plaque than white men. CI = Confidence interval.

Table 4

Associations between Race and Coronary Artery Plaque by HIV Serostatus

Prevalence of Plaque					
Plaque Outcome	Prevalence ratio (95% CI)	P value	Prevalence ratio (95% CI)	P value	HIV interaction P value
	HIV Negative Men (N=383)		HIV Positive Men (N=618)		
		Non-Contrast CT			
Coronary artery calcium	0.94 (0.69–1.31)	0.72	0.75 (0.60–0.94)	0.01	0.32
	N=309	**Contrast CT**	N=450		
Any plaque	1.01 (0.82–1.25)	0.89	0.92 (0.82–1.03)	0.15	0.71
Non-calcified plaque	1.21 (0.91–1.61)	0.18	1.02 (0.87–1.19)	0.82	0.09
Mixed plaque	1.00 (0.62–1.62)	0.99	0.68 (0.50–0.92)	0.01	0.12
Calcified plaque	0.65 (0.42–1.00)	0.051	0.73 (0.54–0.98)	0.04	0.66
Stenosis > 50%	0.74 (0.39–1.40)	0.35	0.51 (0.31–0.85)	0.009	0.19
Extent of plaque Plaque Outcome	Mean Difference	P value	Mean Difference	P value	HIV interaction P value
		Non-Contrast CT			
Coronary artery calcium (N=527)	0.43	0.33	−0.44	0.12	0.14
		Contrast CT			
Total plaque score (N=579)	0.12	0.50	−0.24	0.051	0.005
Non-calcified plaque score (N=449)	0.06	0.69	−0.20	0.10	0.17
Mixed plaque score (N=254)	0.03	0.92	−0.06	0.75	0.15
Calcified plaque score (N=278)	0.19	0.51	0.04	0.86	0.77

Adjusted for age, HIV serostatus, study center, cohort status, CAD risk factors, and measures of socioeconomic status. CAD risk factors include antihypertensive medication use, systolic blood pressure among those not on antihypertensive medications, diabetes medication use, fasting glucose among those not on diabetes medications, use of lipid-lowering medications, total and HDL cholesterol among those not on lipid-lowering medications, body mass index and smoking (pack-years). Measures of socioeconomic status include education, income greater than $50,000 per year, and employment. Prevalence ratio = black men compared to white men. CI = Confidence interval. Analyses of extent of plaque (in natural log scale) include men with plaque present (plaque score > 0).